SYNTHESIS AND CHEMISTRY OF

AGROCHEMICALS III

Edited by

Don R. Baker, Joseph G. Fenyes, and James J. Steffens

ACS Symposium Series 504

ACS SYMPOSIUM SERIES **504**

Synthesis and Chemistry of Agrochemicals III

Don R. Baker, EDITOR
ICI Americas Inc.

Joseph G. Fenyes, EDITOR
Buckman Laboratories International, Inc.

James J. Steffens, EDITOR
E. I. du Pont de Nemours and Company

Developed from symposia sponsored
by the Division of Agrochemicals
of the American Chemical Society

American Chemical Society, Washington, DC 1992

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.fw001

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.fw001

Library of Congress Cataloging-in-Publication Data

Synthesis and chemistry of agrochemicals III / Don. R. Baker, editor, Joseph G. Fenyes, editor, James J. Steffens, editor.

p. cm.—(ACS symposium series, ISSN 0097–6156; 504)

"Developed from symposia sponsored by the Division of Agrochemicals of the American Chemical Society."

Includes bibliographical references and index.

ISBN 0–8412–2473–0

1. Pesticides—Synthesis—Congresses. 2. Herbicides—Synthesis—Congresses. 3. Fungicides—Synthesis—Congresses.

I. Baker, Don R., 1933– . II. Fenyes, Joseph G., 1925– III. Steffens, James J., 1942– . IV. American Chemical Society. Division of Agrochemicals. V. Series.

TP248.P47S964 1992
668'.65—dc20 92–27345
CIP

The paper used in this publication meets the minimum requirements of American National Standard for Information Sciences—Permanence of Paper for Printed Library Materials, ANSI Z39.48–1984. ♾

Copyright © 1992

American Chemical Society

All Rights Reserved. The appearance of the code at the bottom of the first page of each chapter in this volume indicates the copyright owner's consent that reprographic copies of the chapter may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per-copy fee through the Copyright Clearance Center, Inc., 27 Congress Street, Salem, MA 01970, for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to copying or transmission by any means—graphic or electronic—for any other purpose, such as for general distribution, for advertising or promotional purposes, for creating a new collective work, for resale, or for information storage and retrieval systems. The copying fee for each chapter is indicated in the code at the bottom of the first page of the chapter.

The citation of trade names and/or names of manufacturers in this publication is not to be construed as an endorsement or as approval by ACS of the commercial products or services referenced herein; nor should the mere reference herein to any drawing, specification, chemical process, or other data be regarded as a license or as a conveyance of any right or permission to the holder, reader, or any other person or corporation, to manufacture, reproduce, use, or sell any patented invention or copyrighted work that may in any way be related thereto. Registered names, trademarks, etc., used in this publication, even without specific indication thereof, are not to be considered unprotected by law.

PRINTED IN THE UNITED STATES OF AMERICA

American Chemical Society
Library
1155 16th St., N.W.
Washington, D.C. 20036

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.fw001

1992 Advisory Board

ACS Symposium Series

M. Joan Comstock, *Series Editor*

V. Dean Adams
Tennessee Technological University

Mark Arnold
University of Iowa

David Baker
University of Tennessee

Alexis T. Bell
University of California—Berkeley

Arindam Bose
Pfizer Central Research

Robert F. Brady, Jr.
Naval Research Laboratory

Margaret A. Cavanaugh
National Science Foundation

Dennis W. Hess
Lehigh University

Hiroshi Ito
IBM Almaden Research Center

Madeleine M. Joullie
University of Pennsylvania

Mary A. Kaiser
E. I. du Pont de Nemours and Company

Gretchen S. Kohl
Dow-Corning Corporation

Bonnie Lawlor
Institute for Scientific Information

John L. Massingill
Dow Chemical Company

Robert McGorrin
Kraft General Foods

Julius J. Menn
Plant Sciences Institute, U.S. Department of Agriculture

Vincent Pecoraro
University of Michigan

Marshall Phillips
Delmont Laboratories

A. Truman Schwartz
Macalaster College

John R. Shapley
University of Illinois at Urbana–Champaign

Stephen A. Szabo
Conoco Inc.

Robert A. Weiss
University of Connecticut

Peter Willett
University of Sheffield (England)

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.fw001

Foreword

THE ACS SYMPOSIUM SERIES was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of this series is to publish comprehensive books developed from symposia, which are usually "snapshots in time" of the current research being done on a topic, plus some review material on the topic. For this reason, it is necessary that the papers be published as quickly as possible.

Before a symposium-based book is put under contract, the proposed table of contents is reviewed for appropriateness to the topic and for comprehensiveness of the collection. Some papers are excluded at this point, and others are added to round out the scope of the volume. In addition, a draft of each paper is peer-reviewed prior to final acceptance or rejection. This anonymous review process is supervised by the organizer(s) of the symposium, who become the editor(s) of the book. The authors then revise their papers according the the recommendations of both the reviewers and the editors, prepare camera-ready copy, and submit the final papers to the editors, who check that all necessary revisions have been made.

As a rule, only original research papers and original review papers are included in the volumes. Verbatim reproductions of previously published papers are not accepted.

M. Joan Comstock
Series Editor

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.pr001

Preface

IN A WORLD WITH AN EXPANDING POPULATION of approximately 5.5 billion people, where nearly 1.5 billion are underfed or starving, increased production of food crops and fiber is of utmost importance. In addition to natural adversities, such as early frost and drought, crops are also exposed to attack by a variety of fungal, bacterial, and viral diseases and to competition for nutrients by numerous types of weeds. Even after harvest the crop needs protection from deterioration. The importance of using the proper chemical products to ensure a plentiful harvest cannot be emphasized too strongly.

This is the third volume in our continuing effort to bring current information concerning the newest developments in agrochemical research to the attention of those interested in the development of new agrochemicals. As with the previous volumes, our goal is to indicate the current direction of agrochemical research.

This volume, as was its two predecessors, is based on a series of symposia reviewing the discovery of new agrochemicals. These symposia were organized by the editors of these monographs and were sponsored by the Division of Agrochemicals of the American Chemical Society. This book is organized like the preceding volumes. The first chapters deal with the discovery of new plant control agents. The second section deals with control of insects, acarids, and nematodes. The final section covers the control of fungal diseases.

We wish to express our appreciation to all of those who have participated in our symposia and who have shared the results of their work with us. Special thanks go to those who have toiled at writing the chapters that appear in this volume. We hope that our readers will find the contents to be interesting, useful, and, above all, stimulating.

We also wish to thank our employers, Buckman Laboratories International, Inc., E. I. du Pont de Nemours and Company, and ICI

Americas Inc.; without their generous support, this volume and the previous two volumes could not have been published.

DON R. BAKER
ICI Americas Inc.
Richmond, CA 94804

JOSEPH G. FENYES
Buckman Laboratories International, Inc.
Memphis, TN 38108

JAMES J. STEFFENS
E. I. du Pont de Nemours and Company
Stine-Haskell Research Center
Newark, DE 19714

July 6, 1992

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.pr001

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch001

Chapter 1

Progress in a Time of Change

Don R. Baker[1], Joseph G. Fenyes[2], and James J. Steffens[3]

[1]ICI Americas Inc., 1200 South 47th Street, Richmond, CA 94804
[2]Buckman Laboratories International, Inc., 1256 North McLean Boulevard, Memphis, TN 38108
[3]E. I. du Pont de Nemours and Company, Stine-Haskell Research Center, Newark, DE 19714

Agrochemicals continue to be the prime method for controlling insects, plant diseases, and weeds throughout the world and will continue as such for the foreseeable future. The increasing world population will require increased crop production and this will require the use of new environmentally safe and efficacious agrochemicals. Increasing costs of registration and re-registration are causing organizations to reevaluate their products and to discontinue those which are less profitable or have safety difficulties. Increasing pressures for greater product safety provide opportunities for new materials which are safer and more effective. Increasing knowledge about vital enzyme structures are providing greater understanding of interactions with control agents. This is being used in the design of new materials for agriculture. Resistance to agrochemicals by plants, insects, fungi, etc. continues to be a challenge to scientists. More is being learned about the molecular causes of this resistance and in the case of plants this is being used to prepare crop plants which are resistant to certain herbicides. These forces and how they present challenges for those working in the development of new agrochemicals are discussed in this chapter.

A chemist, like a painter or poet, is a maker of concepts. If these concepts are more permanent than theirs, it is because they are made with ideas. Ideas are the core of the chemist's creation. No discussion here can be more than a reflection of each individual undertaking. Moreover, only by studying how the road was traveled in the past can we gain an understanding of the future. The case histories we present here, commercially successful or not, provide that insight into that process which lies behind that creative leap from the old to the new. These considerations have inspired our previous volumes on this subject (*1,2*) and our ongoing ACS Agrochemicals Division Symposium series on which these volumes are based.

0097–6156/92/0504–0001$06.00/0

We seem to be always in a period of change. However, only with change is progress possible. Concern for man himself and his fate must be the chief interest of all technical endeavors. The solutions to these unsolved problems coming from the creations of our minds must be a blessing to mankind and not a curse. The memory of the Silent Spring should be a reminder of our responsibility to future generations.

The Environment for New Agrochemicals

In our lifetime we have seen a tremendous change in how science is perceived in the community (*3*). In the middle decades of the twentieth century science was a major vitality in our society. Scientists ranked high in our community and what they said was believed. Scientific knowledge expanded at a tremendous rate. The world's problems were finding solution through the application of scientific principles. This knowledge was making life easier and better than ever before for many groups in the industrialized world. Even in the developing nations, science in the form of medicine and agriculture was steadily increasing the life span. Hunger was being conquered. Everyone had a conviction that even the most difficult problems were solvable. This was the time of the start of the space and electronic age. For the average person there was more and more time to enjoy life.

Still the same business goes on today, however, many do not have that confidence and conviction that we will continue to find solutions to the world's problems. Today the scientist has lost that stature that he once enjoyed. At the same time various groups in society have developed which are poorly informed about a variety of technical issues. Major decisions are often not made according to rational principles, but by vague intuition or political expediency. The basis of our society is an informed electorate. And with the vast expansion of knowledge most of society today is very poorly informed. To many, the scientist appears to be the foe of both nature and mankind. This view (*3*) is fostered by a media portrayal of everyone being opposed to anything nuclear, chemical or genetically engineered. Any chemical, no matter how safe, is labeled as toxic. If it is not natural it is somehow bad. The media seems to be asking for a risk free society which is just not possible.

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch001

Risk versus Benefit

Mankind has always been faced with a changing variety of risks. Science and technology have contributed toward the reduction of many of the historic major risks. Modern medicine has minimized many of the old health risks. Life expectancy has greatly increased to the point that aging processes are now the major cause of death. Counteracting the effects of aging is the new medical challenge. Modern transportation has made mankind much more mobile. However, the increase in speed has generated a variety of new risks. Technology associated with warfare has brought its own group of risks. Relations between nations are now much more critical for an increasing variety of reasons. There is an expanding list of economic and social risks. The steadily increasing population creates another group of risks. As society becomes more and more complex and interdependent, new risks and problems are created. The benefits of modern civilization are many, however, this has created its own challenges for the future. Increasingly, society seems to be unwilling to accept many of these new risks, however small, even if the benefit is great. With this seems to come an ever increasing resistance to change.

The media has fostered a disproportionate awareness of risks in those areas that create headlines. As an example, if an airliner crashes and kills 100 people, within a few hours most of the world has heard about it. This increased public awareness has contributed toward making air travel by far the safest form of transportation in terms of deaths per mile traveled. The death of a single individual on the highways receives almost no publicity unless the death is unusual for other reasons. And yet there are over 100 deaths each day on the U. S. highways without any apparent recognition. Everyone has heard about Chernobyl and the disaster resulting from that nuclear power plant. However, nuclear power is still the safest form of electric power generation in terms of deaths or injury per megawatt of electric power generated. But what does the public think about the risks of nuclear power?

The politicians of the world in general lean in the direction to which most of their constituencies belong. In the area of risk versus benefit the public is willing to accept large risks in certain areas, and in other areas there is great public reaction to very small risks. In general where the risk involves life style choices much greater risk is accepted by the public. The public knows that hundreds of thousands die each year due to smoking but does very little about it. Alcohol is almost as bad and even less is done by the public. However, in the case of agrochemical food contamination, there is public concern for a risk that is relatively minor. Only relatively recently has the public's attention been focused on the influence of diet and exercise on long term health and well being. This food risk (*4*) is far greater than from agrochemical contamination of our food.

The agrochemical industry responds to these increasing public demands for risk free materials by developing products that meet or exceed these requirements. However, the costs are great to discover and develop these new alternative products. Because of these increased costs in registration and re-registration, only those superior products which are expected to have large markets have sufficient potential for profit to warrant the costs necessary for their development. In the light of these increased costs in the registration and re-registration of products, many organizations are dropping the registrations on those materials that are less profitable. For farmers growing so-called minor crops, this usually means that there are fewer and fewer materials that are available and registered for use on these crops.

In any risk benefit analysis dealing with these major issues of society such as nuclear power, genetic manipulation, and use of agrochemicals the question becomes "What is the acceptable risk?" In the light of other risks that everyone faces each day, the risks inherent with agrochemicals must be evaluated (*4-7*). As an example, consider the risk of cancer which is many times greater when eating broiled meat once a week as compared to eating an apple each week with a certain pesticide residue. What level of risk is perceived as acceptable?

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch001

Agrochemical Safety

In our previous volume we referred to the changing picture concerned with agrochemical safety. Earlier we have discussed risk-benefit as it relates to development of new products. This situation has come about by the changing standards; new laws and regulations at both the federal and state level. Even local governments are making their own regulations. These new laws and regulations have greatly increased the costs associated with the registration and manufacture of agrochemicals in the U. S. Manufacturers are forced to consider which products to support in light of the time and effort needed for continued registration of the product. Some new tests cost millions of dollars for just one environmental investigation. Only those products worthy of such costs continue to be registered. For the development of new materials these new environmental requirements such as leaching, soil persistence, volatility, and soil surface loss are important considerations. These structure-environmental fate and structure-toxicity relationships now enter very early in the development of new products. Modes of action that are peculiar to a pest are the major choice for materials which are safe from a toxicity standpoint. The prime targets are those systems which require small amounts of compounds so as to reduce the environmental impact on other systems.

The cause of these increasing regulatory expenses is the public perception of a suspected problem. Is our food safe? Is the environment safe? Education is clearly needed so that the public understands just what the food and environmental risks are and can put them into perspective. The agrochemical industry needs to abandon its traditional reserve and put safety issues to the public in a form that can be understood.

Resistance

Pest resistance to chemicals has long been known. No class of agrochemical is unaffected. More and more resistance is coming to be understood (*8,9*), even -- in some cases -- its biochemical and molecular genetic basis. Single site compounds which interact with an enzyme noncompetitively, or uncompetitively with respect to substrate are potentially very troublesome, since a resistant species may be as fit as the susceptible form (*10*). A similar concern applies to forms which owe their resistance to enhanced metabolism (*11,12*). On the other hand, evidence has shown that, at least with Photosystem II herbicides, strains resistant by virtue of mutation at the site of binding of competitive inhibitors may be less fit in the environment in the absence of selection pressure (*13*). Compounds, which have as their mode of action an effect at multiple sites in the organism, develop resistance much more slowly. The major problem with this type compound is the fact that it may also effect sites in non-target species and there is then the potential for toxicology problems.

Historically, most of the broad spectrum foliar fungicides were types which effect multiple sites in the fungi. Resistance is slow to develop for these materials. However, most of these compounds have toxicology problems of one type or another. Resistance management strategies are evolving to accommodate these various types.

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch001

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch001

This knowledge about the molecular changes occurring in resistant organisms is an aid to the molecular biologists to develop crop plants which are resistant to a particular herbicide. (*14,15*)

Discovery Designs

Making new compounds is at the heart of the discovery process for the agricultural chemist. In our last volume we describe the four basic approaches for compound design. These approaches have changed little in the intervening time.

The approach involving the synthesis of enzyme target site directed inhibitors inhibitors has yet to yield a commercial success in agricultural chemistry, although several classes of potent herbicides have been shown after the fact to be target site directed (*16*). In spite of this lack of commercial success, we can nevertheless be encouraged by a growing number of comparable successes in the field of pharmaceutical chemistry (*17*), and thus inhibitors of specific enzymes are now receiving increasing attention from crop protection chemists (*18*). The chapter by Basarab et al. in this volume discusses some recent progress in designing inhibitors of a fungal sterol reductase. The chapter by Yamaki et al. is an example of an effort to better understand an important enzyme, and what is involved in enzyme binding in order to design more effective control agents of potential agrochemical utility.

The number of cases in which natural products have provided leads to commercially successful crop protection chemicals have, in the past, been few in number but significant in scope -- most notably the development of modern synthetic pyrethroids from pyrethrin and more recently the avermectin family of compounds. This use of natural products as models appears to be gaining momentum as numerous leads of biological origin are uncovered (*19,20*), and several papers in this volume attest to the success of this approach.

Conclusions

We continue to be optimistic about the future of agricultural chemistry. With the resistance problem in all areas of interest there is the continuing need to find highly active materials which also control resistant species. Understanding the molecular biology of resistant species offers the hope of devising materials which overcome the resistance problem. Also, the search goes on for new biological systems which can be affected at low levels by control compounds. Environmental concerns too are creating the need for new materials which have little environmental impact. This is adding a new dimension to what is needed for an acceptable profitable new material. As these chapters show, the search has truly become international. Agrochemistry continues to attract creative chemists to the adventure so necessary to our civilization.

Acknowledgments

We express our appreciation to the ACS Agrochemical Division Executive Committee and Program Committee for their continued support of our efforts for the Symposium Series which forms the basis for this book. Also we are grateful for the ACS Books

Department for their timely publication of the efforts resulting from these symposia. Particularly thanks are due Anne Wilson of ACS Books for her help throughout the whole editorial process. And above all, we express our thanks to those scientists the world over who have generously shared their experiences with the agricultural community in this volume.

Literature Cited

1. *Synthesis and Chemistry of Agrochemicals*; Baker, D. R.; Fenyes, J. G.; Moberg, W. K.; Cross, B., Eds.; ACS Symposium Series No. 355; American Chemical Society: Washington, DC, 1987.
2. *Synthesis and Chemistry of Agrochemicals II*; Baker, D. R.; Fenyes, J. G.; Moberg, W. K., Eds.; ACS Symposium Series No. 443; American Chemical Society: Washington, DC, 1991.
3. Mohr, H. In *Pesticide Chemistry: Advances in International Research, Development, and Legislation; Proceedings of the Seventh International Congress of Pesticide Chemistry (IUPAC), Hamburg 1990*; Frehse, H., Ed.; VCH Publisher Inc., New York, 1991; pp 21-33.
4. Ames, B. N.; Magaw, R.; Gold, L. S.; *Science* **1987**, *236*, 271-280.
5. LeBaron, H. M. *Weed Technology* **1990**, 4, 671-689.
6. Bidinotto, R. J. *Readers Digest* **October 1990**, 53-58.
7. Brookes, W. T. *The High Costs of "Political Science."* American Industrial Health Council, 1991 Annual Meeting, December 5, 1991, ANA Hotel, Washington DC.
8. *Managing Resistance to Agrochemicals*; Green, M. B., LeBaron, H. M., Moberg, W. K., Eds.; ACS Symposium Series No. 421;American Chemical Society: Washington, DC, 1990.
9. *Herbicide Resistance in Weeds and Crops*; Caseley, J. C.; Cussans, G. W.; Atkin, R. K., Eds.; Long Ashton International Symposium; Butterworth-Heineman: Oxford, 1991.
10. Schloss, J. V. In *Target Sites for Herbicide Action*; Boeger, P.; Sandmann, G., Eds.; CRC Press: Boca Raton, 1989, pp 221-223.
11. Brattsten, L. B. In *Managing Resistance to Agrochemicals*; Green, M. B.; LeBaron, H. M.; Moberg, W. K., Eds.; ACS Symposium Series No. 421; American Chemical Society: Washington, DC, pp 42-60.
12. Powles, S. B.; Holtum, J. A. M.; Matthews, J. M.; Liljegren, D. R. In *Managing Resistance to Agrochemicals*; M. B. Green, LeBaron, H. M.; Moberg, W. K., Eds.; ACS Symposium Series No. 421; American Chemical Society: Washington, DC, pp 394-406.
13. Holt, J. S. In *Managing Resistance to Agrochemicals*; Green, M. B.; LeBaron, H. M.; Moberg, W. K., Eds.; ACS Symposium Series No. 421; American Chemical Society: Washington, DC, pp 419-429.
14. Mazur, B. J.; Falco, S. C. *Ann. Rev. Plant Physiol. Plant Mol. Biol.* **1989**, *40*, 441.
15. Stalker, D. M. In *Target Sites for Herbicide Action*; Boeger, P.; Sandmann, G., Eds.; CRC Press: Boca Raton, 1989, pp 147-164.

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch001

16. Schloss, J. V. In *Target Sites for Herbicide Action*; Boeger, P.; Sandmann, G., Eds.; CRC Press: Boca Raton, 1989, pp 165-245.
17. *Design of Enzyme Inhibitors as Drugs*; Sandler, M.; Smith, H. J., Eds.; Oxford University Press: Oxford, 1989.
18. *Prospects for Amino Acid Biosynthesis Inhibitors in Crop Protection and Pharmaceutical Chemistry*; Copping, L. G.; Dalziel, J.; Dodge, A. D., Eds.; BCPC Monograph No. 42; British Crop Protection Council: Farnham, Surrey, UK, 1989.
19. Boeger, P. In *Target Sites for Herbicide Action*; Boeger, P.; Sandmann, G., Eds.; CRC Press: Boca Raton, 1989, pp 247-282.
20. Cremlyn, R. J. *Agrochemicals. Preparation and Mode of Action*; John Wiley & Sons: Chichester, UK, 1991, pp 53-78.

RECEIVED May 13, 1992

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch001

Downloaded by UNIV OF GUELPH LIBRARY on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch002

Chapter 2

1,2,4-Triazolo[1,5-*a*]pyrimidine-2-sulfonanilide Herbicides

Influence of Alkyl, Haloalkyl, and Halogen Heterocyclic Substitution on In Vitro and In Vivo Biological Activity

William A. Kleschick[1], Mark J. Costales[2], B. Clifford Gerwick[1], J. B. Holtwick[2], R. W. Meikle[2], W. T. Monte[2], N. R. Pearson[2], S. W. Snider[2], M. V. Subramanian[2], J. C. VanHeertum[2], and A. P. Vinogradoff[2]

[1]Discovery Research, DowElanco Research Laboratories, P.O. Box 708, Greenfield, IN 46140
[2]Discovery Research, DowElanco Research Laboratories, P.O. Box 9002, Walnut Creek, CA 94598

An outline of the synthetic routes used to prepare a series of alkyl, halo and haloalkyl substituted 1,2,4-triazolo[1,5a]-pyrimidine-2-sulfonanilides is presented. The *in vitro* activity against acetolactate synthase and the herbicidal activity of these analogs is discussed. The evaluation of these activities led to the selection of DE-498 as a candidate for development as a broadleaf herbicide for soybeans, corn and other crops.

The discoveries of the sulfonylurea and the imidazolinone classes of herbicides represent important advances in technology for weed control (*1*, *2*). The attributes of the high levels of herbicidal activity, application flexibility, excellent margins of crop tolerance and low levels of toxicity to mammals exhibited by these compounds are important characteristics for modern agrochemicals. The performance characteristics of these materials are linked in part to the mechanism of action of the disruption of the biosynthesis of amino acids in plants (*3*). The site of action, the enzyme acetolactate synthase (ALS, EC 4.1.3.18) in the pathway to the branched chain amino acids, displays a sensitivity to a number of structural classes of compounds (*4*).

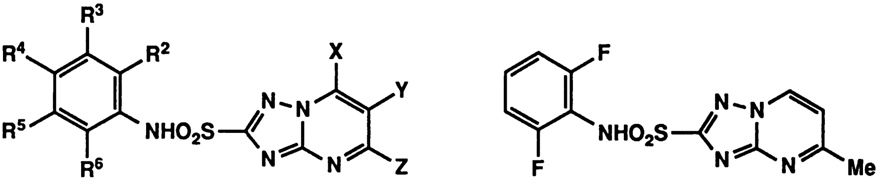
The 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonanilides (**1**, Figure 1) are a new class of highly active herbicides (*5*, *6*). These compounds also act by disrupting the biosynthesis of branched chain amino acids in plants through the inhibition of ALS (*7*). One member of this class, DE-498 (**2**), has been advanced to the final stages of development. This report details the structure activity studies on the triazolopyrimidine ring in **1** leading to the selection of DE-498 as a development candidate.

Results and Discussion

Synthetic Routes. An outline of the general synthetic route to triazolopyrimidine sulfonanilides applicable to the synthesis of many compounds is illustrated in Figure 2 (*8*). 3-Amino-5-mercapto-1,2,4-triazole (**3**) or the corresponding benzylthioether (**4**) (*9*) is condensed with a 1,3-dicarbonyl compound or operational equivalent of a 1,3-dicarbonyl compound to afford triazolopyrimidines **5** or **6** respectively. Oxidative chlorination of **5** or **6** in aqueous acid media produces the sulfonyl

0097–6156/92/0504–0010$06.00/0

chloride (**7**) which is reacted with the appropriate aniline in the presence of an acid scavenger (e.g. pyridine) to give **1**.



1 **2**

Figure 1. 1,2,4-Triazolo[1,5-a]pyrimidine-2-sulfonanilides **1** and **2**.

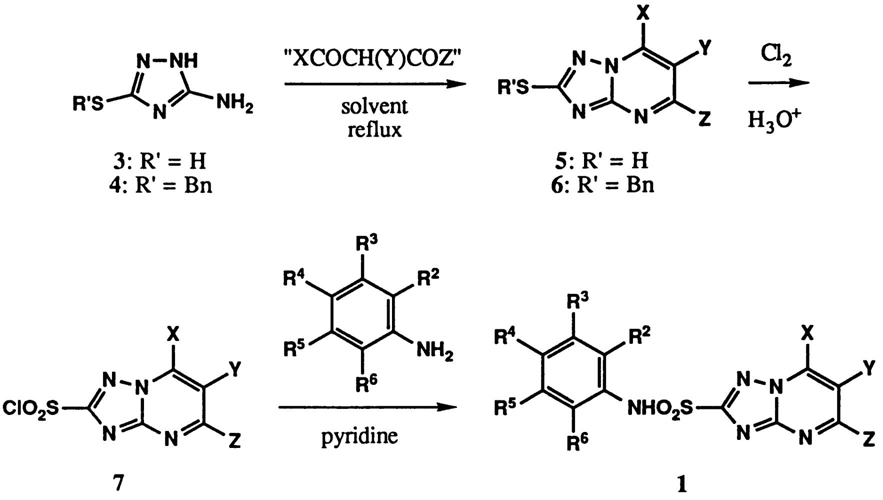


Figure 2. General synthetic route to 1,2,4-triazolo[1,5-a]pyrimidine -2-sulfonanilides.

The method outlined in Figure 2 can be employed to prepare a wide variety of compounds derived from symmetrically substituted 1,3-dicarbonyl compounds. However, the outcome of the first step in the reaction sequence may not be straightforward in reactions with unsymmetrically substituted 1,3-dicarbonyl compounds. Figure 3 illustrates our results in condensation reactions of **4** with a variety of unsymmetrically substituted 1,3-diketones (*10*). In all of these instances some measure of regiochemical control was observed in the reactions. Compounds **8** and **12** were isolated in good yield through one recrystallization of the crude product. Compounds **10** and **11** were isolated by chromatography. The structures of **8** and **10** were established by single crystal X-ray analysis. The structures of **12** and **13** were established by a synthesis of **13** by an unambiguous route as illustrated in Figure 4 (*10*). Reaction of **4** with ethyl cyclopentanone-2-carboxylate gave triazolopyrimidine **14** which was converted to the chloro substituted compound **15**

Downloaded by UNIV OF GUELPH LIBRARY on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch002

Downloaded by UNIV OF GUELPH LIBRARY on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch002

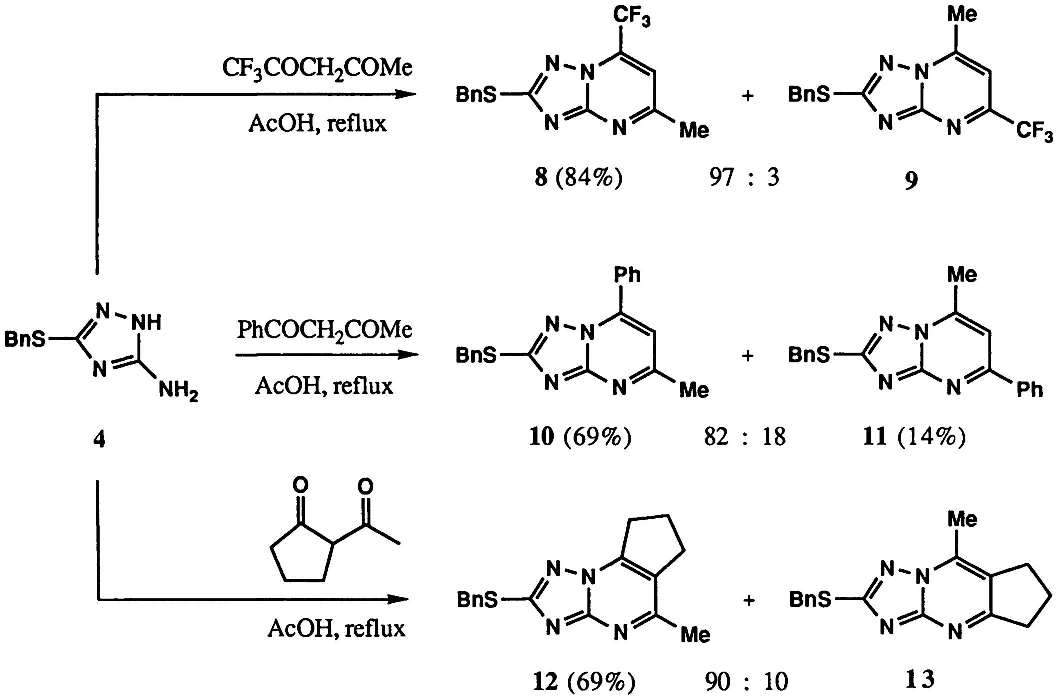

BnS
N
NH
N
NH2
4
CF3COCH2COMe
AcOH, reflux
PhCOCH2COMe
AcOH, reflux
O
O
AcOH, reflux
CF3
Me
8 (84%)
97 : 3
9
Ph
Me
10 (69%)
82 : 18
11 (14%)
Ph
12 (69%)
90 : 10
13
+

Figure 3. Reaction of **4** with unsymmetrical 1,3-diketones.

Downloaded by UNIV OF GUELPH LIBRARY on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch002

with $POCl_3$. Reaction of **15** with methyl magnesium bromide gave **13** in good overall yield.

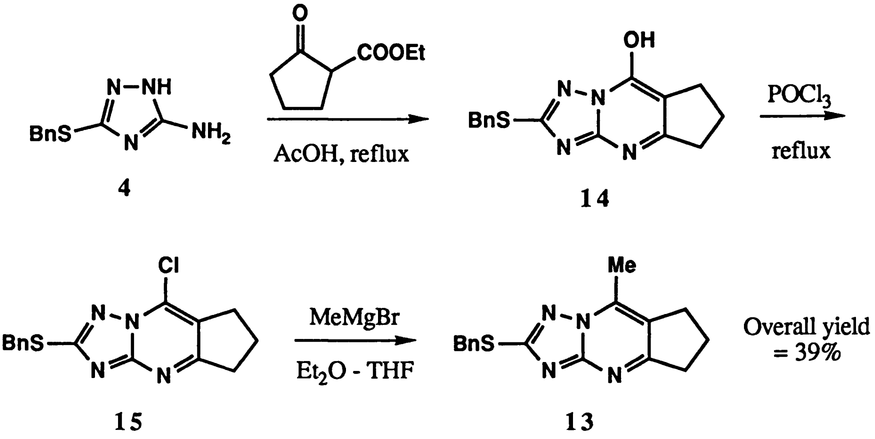

BnS
N–NH
N
NH2
4
O
COOEt
AcOH, reflux
OH
N
14
POCl3
reflux
Cl
15
MeMgBr
Et2O - THF
Me
13
Overall yield
= 39%

Figure 4. Unambiguous synthesis of **13**.

The reaction of **4** with ketoaldehyde derivatives is more complex (*11*). Reaction of **4** with acetylacetaldehyde dimethyl acetal under conventional reaction conditions leads to 2:1 mixture of **16** and **17** (Figure 5). If **4** is added slowly to the reaction mixture regiochemical control is achieved and **17** is isolated in good yield. The regioselection of the reaction can be reversed by conducting the reaction under basic conditions. In this instance **16** is produced as the sole product of the reaction in good yield (Figure 6). The structure of **16** was confirmed by single crystal X-ray

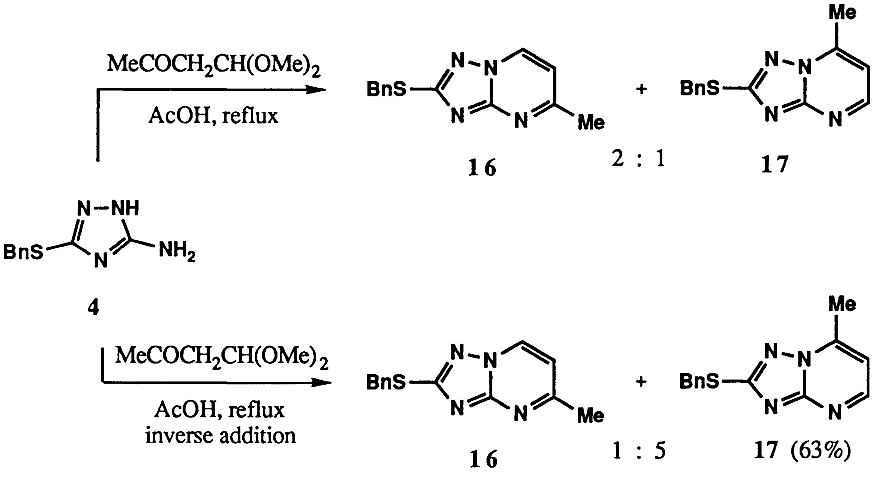
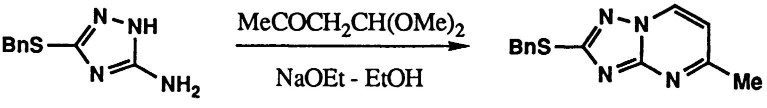

MeCOCH2CH(OMe)2
AcOH, reflux
BnS
N–NH
NH2
4
N
Me
16
+
2 : 1
17
MeCOCH2CH(OMe)2
AcOH, reflux
inverse addition
1 : 5
17 (63%)

Figure 5. Reaction of **4** with acetylacetaldehyde under acidic conditions.



4 **16** (74%)

Figure 6. Reaction of **4** with acetylacetaldehyde under basic conditions.

analysis. Analogous regioselection is observed in reactions with other ketoaldehydes and derivatives (i.e. sodium salts) under basic conditions (*12*). Intermediates **8**, **10**, **11**, **12**, **13**, **16**, **17** and related compounds prepared by similar methods can be converted to **1** by the methods outlined in Figure 2.

Biological Testing. The biological activity of a series of triazolopyrimidine sulfonanilides derived from 2,6-dichloroaniline was determined. The *in vivo* and *in vitro* data summarized in Table I are expressed as the average concentration required to achieve 50% growth inhibition (GR_{50}) of five broadleaf weed species (*Abutilon, Amaranthus, Datura, Ipomoea* and *Xanthium*) and the concentration to achieve 50% inhibition (I_{50}) of ALS. These data indicate a lack of correlation between enzyme inhibition and whole plant response for this series of compounds. The failure of some of the more potent enzyme inhibitors (i.e. **1**: X, Y = $-CH_2CH_2CH_2-$; Z = Me; $R^2 = R^6 = Cl$; $R^3 = R^4 = R^5 = H$) to translate their activity in whole plants is most likely a consequence on poor uptake, poor translocation, metabolic detoxification or a combination of these factors.

One of the compounds represented in Table I (i.e. **1**: X = Y = H, Z = Me; $R^2 = R^6 = Cl$; $R^3 = R^4 = R^5 = H$) exhibited selectivity to several major crops including soybean, corn and wheat in addition to high levels of activity against a number of broadleaf weeds. Further optimization by variation of R^2 and R^6 led to the discovery of DE-498 (**2**) as a candidate for development. The optimization process involved examining a large number of highly active combinations of R^2 and R^6 in which one or both of the substituents were electron withdrawing groups. DE-498 was selected as the most promising candidate from this series of compounds based on a combination of factors including herbicidal activity, crop selectivity and environmental behavior. The proposed common name for DE-498 is flumetsulam.

.In soil applications (pre-plant incorporated, PPI) DE-498 controls *Abutilon* (velvetleaf), *Amaranthus* (pigweed), *Chenopodium* (lambsquarters), *Portulaca* (purslane), *Raphanus*, *Sida* (teaweed) *and Solanum* (nightshade) at 35 g/ha. At 70 g/ha PPI *Acanthospermum* (starbur), *Ambrosia* (ragweed), *Bidens*, *Datura* (jimsonweed), *Desmodium* (beggarweed), *Helianthus* (sunflower), *Ipomoea hederaceae* (ivy leaf morningglory), *Polygonum* (smartweed) and *Xanthium* (cocklebur) are controlled. *Commelina* and *Ipomoea lacunosa* (pitted morningglory) are not controlled by DE-498 at PPI application rates of 70 g/ha and below.

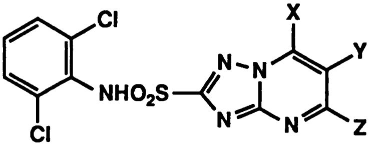
In foliar applications DE-498 controls *Abutilon, Datura, Portulaca, Raphanus, Sida* and *Solanum* at 17 g/ha. At 35 g/ha in a postemergence application *Acanthospermum, Amaranthus, Ambrosia, Bidens, Chenopodium, Desmodium, Helianthus, Polygonum* and *Xanthium* are controlled. *Commelina, Ipomoea hederaceae*, and *Ipomoea lacunosa* are not controlled by DE-498 at postemergence application rates of 35 g/ha and below.

The tolerance of DE 498 to major crops in PPI and postemergence applications is illustrated in Table II. Barley, wheat and corn all demonstrate high levels of tolerance to soil and foliar applications. Soybeans exhibit a high level of tolerance to soil applications and a modest degree of tolerance to foliar applications. The broad

Downloaded by UNIV OF GUELPH LIBRARY on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch002

Downloaded by UNIV OF GUELPH LIBRARY on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch002

Table I. *In vivo* and *in vitro* activity of a series of triazolopyrimidine sulfonanilides



X	Y	Z	GR_{50} (ppm)	I_{50} (µM)
Me	H	Me	3	0.060
H	H	Me	5	0.11
Me	H	H	10	1.8
H	Cl	H	27	0.48
CF_3	H	Me	33	0.23
H	H	H	37	6.6
H	Me	H	48	0.19
Me	Me	Me	54	0.41
$-CH_2C$	H_2CH_2-	Me	740	0.044
H	Me	Me	920	0.24
Me	Cl	Me	1000	1.0
CF_3	H	CF_3	≥ 2000	8.6
H	H	Et	≥ 2000	0.27
H	H	*i*-Pr	≥ 2000	0.25

Table II. Crop tolerance to foliar and soil applications of DE-498 in greenhouse bioassays

Crop	Foliar Application GR_{10} Value (g/ha)	Soil Application GR_{10} Value (g/ha)
Corn	>70	50
Wheat	>70	>70
Barley	>70	>70
Soybeans	20	>70
Rice	15	22
Sunflower	12	11
Cotton	7	4
Sugarbeet	3	5
Rape	3	4

spectrum activity of DE-498 in combination with selectivity to a variety of major agronomic crops offers a multitude of opportunities for selective weed control. The basis of selectivity of DE-498 to corn and soybeans is metabolic detoxification (*13*). In soybean the detoxification is initiated by a process which results in disruption of the pyrimidine portion of the triazolopyrimidine ring. In corn the process involves an initial hydroxylation of the methyl group at the 5-position on the triazolopyrimidine ring.

DE-498 possesses a favorable toxicological profile. The acute toxicity of DE-498 is very low. No dermal sensitization and only slight eye irritation has been observed. No mutagenic or teratogenic effects have been found with DE-498.

Conclusion

DE-498 combines broad spectrum herbicidal activity with selectivity to multiple major crops. In addition it possesses low toxicity to mammals, safety to key rotational crops and favorable environmental behavior (*14*). The combination of these attributes render DE-498 a useful, new tool for selective weed control in a variety of major crops.

Literature Cited

1. Sauers, R. F.; Levitt, G., In *Pesticide Synthesis through Rational Approaches,* Magee, P. S.; Kohn, G. K.; Menn, J. J., Eds.; ACS Symposium Series 255, American Chemical Society: Washington, D.C., 1984, p. 21-28.
2. Los, M., In *Pesticide Science and Biotechnology*, Greenhalgh, R.; Roberts, T. R., Eds.; Blackwell Scientific Publications: Oxford, 1987, p. 35-42.
3. LaRossa, R. A.; Falco, S. C. *Trends in Biotechnology* **1984**, *2*, 158-161.
4. Schloss, J. V.; Ciskanik, L. M.; VanDyk, D. E. *Nature* **1988**, *331*, 360-362.
5. Kleschick, W. A.; Gerwick, B. C., In *Prospects for Amino Acid Biosynthesis Inhibitors in Crop Protection and Pharmaceutical Chemistry,* Copping, L. G.; Dodge, A. D.; Dalziel, J., Eds.; British Crop Protection Council Monograph No. 42, Lavenham Press Limited: Lavenham, Suffolk, 1989, p. 139-146.
6. Kleschick, W. A.; Costales, M. J.; Dunbar, J. E.; Meikle, R. W.; Monte, W. T.; Pearson, N. R.; Snider, S. W.; Vinogradoff, S. W. *Pestic. Sci.* **1990**, *29*, 341-355.
7. Gerwick, B. C.; Subramanian, M. V.; Loney-Gallant, V. I.; Chandler, D. P. *Pestic. Sci.* **1990**, *29*, 357-364.
8. For the first example of the use of this route to prepare 5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonanilide, see: Broadbent, W; Miller, G. W.; Rose, L. British Patent 951,652, **1964**.
9. O'Brien, D. E.; Novinson, T.; Springer, R. H. U.S. Patent 4,036,840, **1977**.
10. Kleschick, W. A.; Bordner, J. *J. Heterocycl. Chem.* **1989**, *26*, 1489-1493.
11. Monte, W. T.; Kleschick, W. A.; Meikle, R. W.; Snider, S. W.; Bordner, J. *J. Heterocycl. Chem.* **1989**, *26*, 1393-1396.
12. Monte, W. T.; Kleschick, W. A.; Bordner, J. unpublished results.
13. Swisher, B. A.; Gerwick, B. C.; Cheng, M.; Miner, V. W.; deBoer, G. J. *Abstr. Meet. Weed Sci. Soc. Am.* **1991**, *31*, 50.
14. For a detailed discussion of the soil behavior of DE-498, see: Fontaine, D. D.; Lehmann, R. G.; Miller, J. R. *J. Environ. Qual.* **1991**, *20*, 759-762.

RECEIVED June 30, 1992

Downloaded by UNIV OF GUELPH LIBRARY on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch002

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

Chapter 3

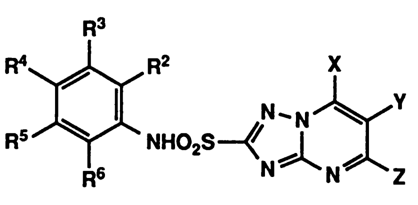
1,2,4-Triazolo[1,5-*a*]pyrimidine-2-sulfonanilide Herbicides

Influence of Alkoxy Heterocyclic Substitution on In Vitro and In Vivo Biological Activity and Soil Decomposition

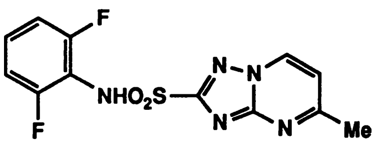
William A. Kleschick[1], C. M. Carson[1], Mark J. Costales[2], J. J. Doney[2], B. Clifford Gerwick[1], J. B. Holtwick[2], R. W. Meikle[2], W. T. Monte[2], J. C. Little[2], N. R. Pearson[2], S. W. Snider[2], M. V. Subramanian[2], J. C. VanHeertum[2], and A. P. Vinogradoff[2]

[1]Discovery Research, DowElanco Research Laboratories, P.O. Box 708, Greenfield, IN 46140
[2]Discovery Research, DowElanco Research Laboratories, P.O. Box 9002, Walnut Creek, CA 94598

The 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonanilide herbicides (**1**, Figure 1) are a new class of highly active acetolactate synthase (ALS) inhibiting herbicides (*1, 2, 3*). In the preceding chapter we described initial structure activity studies in this series focussed on the impact of substitution of the heterocyclic ring with alkyl groups, haloalkyl groups and halogens. From this effort came the discovery of DE-498 (**2**) which has been advanced to the final stages of development. The proposed common name for DE-498 is flumetsulam. DE-498 is effective in controlling a wide variety of broadleaf weed species with selectivity to major crops such as corn, soybean and wheat. This report details the synthesis and structure activity studies surrounding alkoxy substituted 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonanilides.



1



2

Figure 1. 1,2,4-Triazolo[1,5-a]pyrimidine-2-sulfonanilides **1** and **2**.

Results and Discussion

Synthetic Routes. General routes to alkoxy substituted 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonanilides are illustrated in Figure 2. Aminotriazole **3** reacts with ethyl acetoacetate to give triazolopyrimidine **4**. Compound **4** reacts with phosphorous

0097–6156/92/0504–0017$06.00/0

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

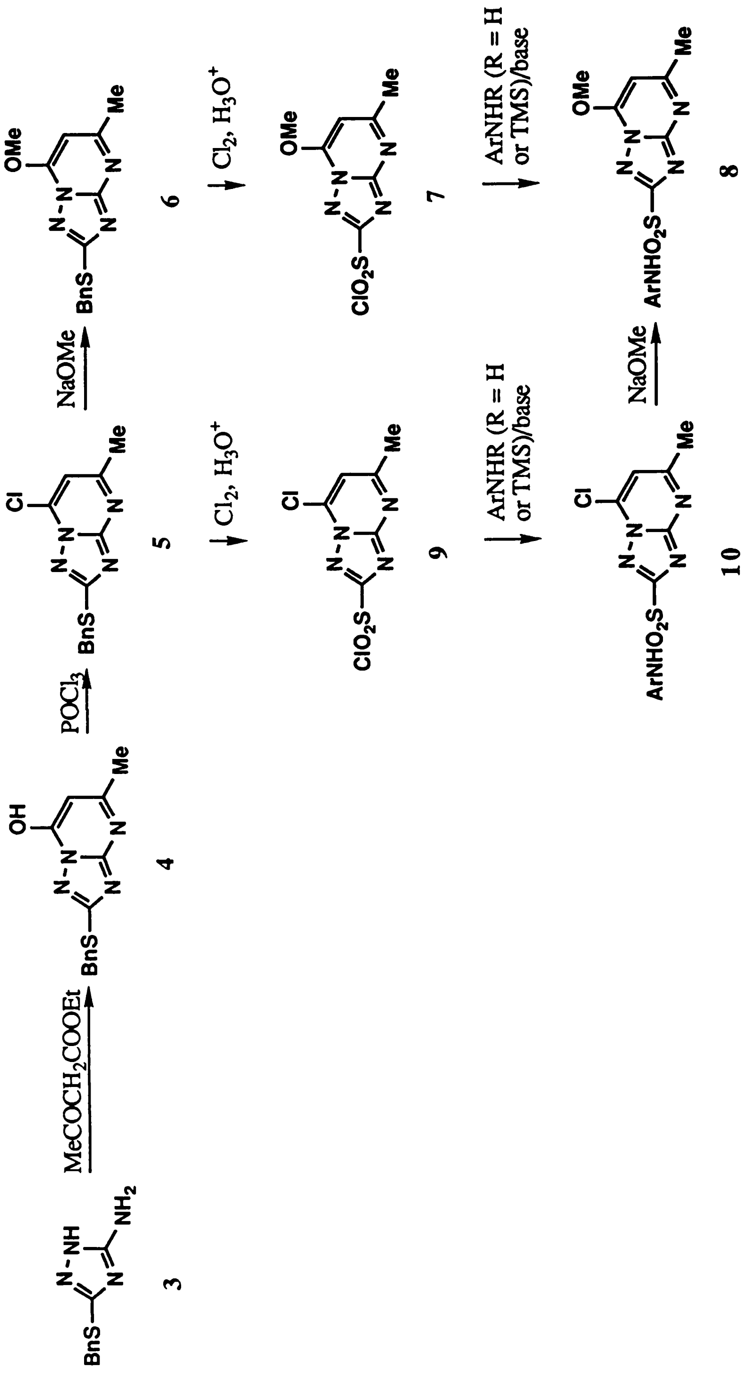

BnS
N-NH
N
NH2
3
MeCOCH2COOEt
BnS
N-N
N
N
OH
Me
4
POCl3
BnS
Cl
Me
5
NaOMe
BnS
OMe
Me
6
Cl2, H3O+
ClO2S
Cl
Me
9
ClO2S
OMe
Me
7
ArNHR (R = H or TMS)/base
ArNHO2S
Cl
Me
10
NaOMe
ArNHO2S
OMe
Me
8

Figure 2. Synthetic routes to 7-alkoxy-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonanilides

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

oxychloride to produce chloro compound **5**, and the halogen in **5** reacts readily with sodium methoxide to yield **6**. Conversion of **6** to the sulfonyl chloride **7** is achieved by reaction with chlorine in aqueous acidic media (e.g. aqueous acetic acid or hydrochloric acid). Final conversion of the sulfonyl chloride **7** to sulfonanilide **8** is accomplished by reaction with the appropriate aniline or silylated aniline derivative (*4*) in the presence of base (e.g. pyridine). In some instances it is desirable to conduct coupling reactions of the appropriate aniline or silylated aniline derivative with the more reactive sulfonyl chloride **9** to produce sulfonanilide **10**. Compound **10** is converted smoothly to **8** by reaction with excess sodium methoxide. The routes outlined in Figure 2 is general and can be employed to prepare analogs of **8** in which the functional group at the 7-position is introduced *via* a nucleophilic substitution reaction of **5** or **10**. In addition substituting malonic esters for ethyl acetoacetate in the reaction sequence leads to **1** (e.g. X = Y = OMe) in which both X and Y are introduced *via* the reaction of nucleophiles (e.g. NaOMe) with **1** in which X and Y are chlorine.

In some situations the route shown in Figure 2 leads to low yields of **8**. Long reaction times associated with relatively unreactive anilines which contain several electron withdrawing groups are incompatible with the stability of **8** to conditions for the coupling reaction. As a consequence routes which proceeded *via* formation of a 3-amino-1,2,4-triazole-5-sulfonanilide (**11**) followed by formation and elaboration of the pyrimidine ring were explored (Figure 3).

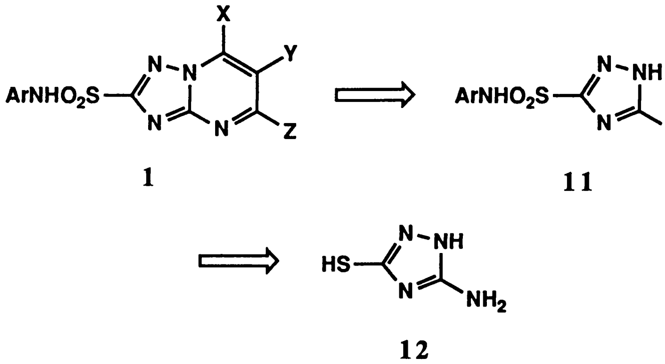


Figure 3. Retrosynthetic analysis for an alternative route to **1**.

Several routes to key intermediate **11** have been devised. The first route illustrated in Figure 4 employs an oxidative degradation of a dimethyl triazolopyrimidine ring (*5*). Oxidation of **13** with hydrogen peroxide under basic conditions afforded acetamide **14** which was subsequently hydrolyzed to **15** in an overall yield of 56%.

Figure 5 shows a route to intermediate **11** which employs a strategy involving a protecting group (*6*). Amino mercapto triazole **12** reacts with benzoyl chloride in pyridine to afford the benzamide **16** which was converted to the sulfonyl chloride **17** under standard conditions. Coupling of **17** with excess 2,6-difluoroaniline gave **18** which was hydrolyzed to afford **19**. The overall yield for this process was 34%.

The last approach to intermediate **11** involves a direct chlorine oxidation of 3-amino-5-mercapto-1,2,4-triazole **12** is shown in Figure 6 (*7*). Compound **12** was reacted with chlorine in aqueous HCl to afford sulfonyl chloride **20** which was isolated as the hydrochloride salt. Coupling of **20** with excess 2,6-difluoroaniline afforded **19** in *98% overall yield.*

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

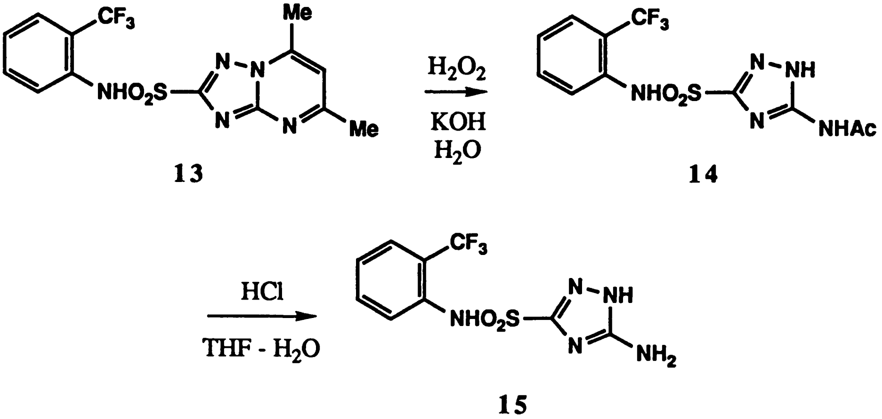

CF3
NHO2S
N-N
Me
Me
13
H2O2
KOH
H2O
N-NH
NHAc
14
HCl
THF - H2O
NH2
15

Figure 4. Synthesis of 3-amino-1,2,4-triazole-5-sulfonanilide **15** *via* oxidative degradation of a triazolopyrimidine.

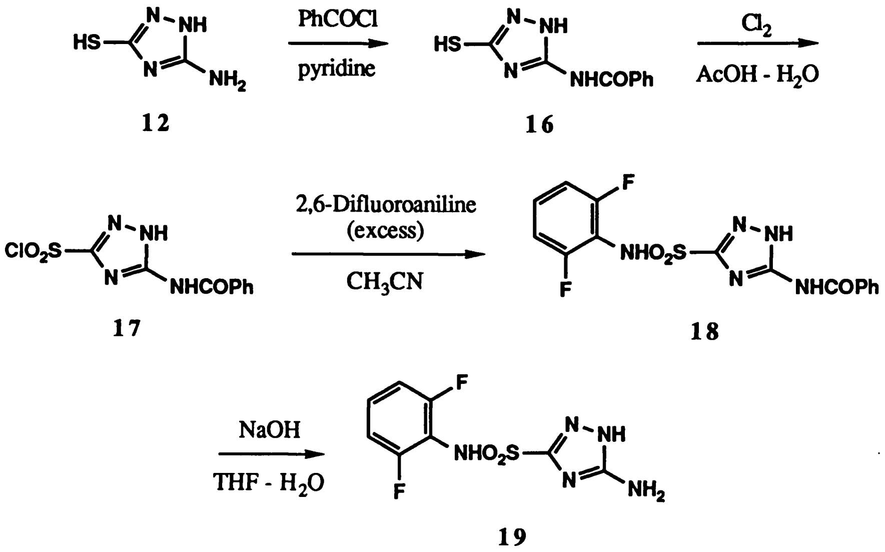

HS
N-NH
NH2
12
PhCOCl
pyridine
NHCOPh
16
Cl2
AcOH - H2O
ClO2S
17
2,6-Difluoroaniline
(excess)
CH3CN
F
NHO2S
18
NaOH
THF - H2O
19

Figure 5. Synthesis of 3-amino-1,2,4-triazole-5-sulfonanilide **19** using a protecting group strategy.

Figure 7 illustrates the utility of 3-amino-1,2,4-triazole-5-sulfonanilides (**11**) in the synthesis of 1,2,4-triazolo[1,5-a]-pyrimidine sulfonanilides (**1**). Triazole sulfonanilide **21** reacts with dimethyl malonate under basic conditions to form triazolopyrimidine sulfonanilide **22**. Compound **22** can be converted to 5,7-dimethoxy triazolopyrimidine sulfonanilide **24** under standard conditions *via* the intermediate dichloro compound **23**. In a similar manner **21** can be converted to the

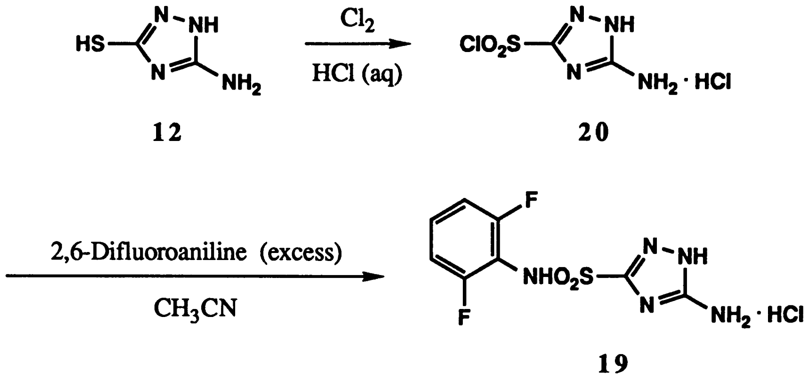


Figure 6. Synthesis of 3-amino-1,2,4-triazole-5-sulfonanilide **19** through direct chlorine oxidation of **12**.

7-methoxy-5-methyl triazolopyrimidine **27** *via* the intermediate 7-hydroxy-5-methyl and 7-chloro-5-methyl compounds **25** and **26**. A variety of additional triazolopyrimidine sulfonanilides can be prepared by the protocol outlined in Figure 7. These include materials with amino, alkylamino, dialkylamino and alkylthio substitution at the 5- and 7-positions of the triazolopyrimidine ring.

Biological Tests. The biological activity of a series of alkoxy substituted analogs in comparison to two alkyl substituted analogs is shown in Table I. The herbicidal activity is expressedin the average concentration to achieve 50% growth inhibition on broadleaf weeds (GR_{50}). The *in vitro* activity is expressed in the concentration required to achieve 50% inhibition of ALS (I_{50}). The *in vitro* activity against ALS is significantly greater for the alkoxy substituted compounds. However, these inherent activity differences are diminished *in vivo*. For example, whereas the dimethoxy analog (X = Y = OMe) is approximately twenty four times more active than the dimethyl (X = Y = Me) analog as an enzyme inhibitor, it is only five times more active as a herbicide.

The soil decomposition of herbicides is an important issue in modern agriculture. We have studied the effect of changes in the structure of the triazolopyrimidine sulfonanilides on the rates of soil decomposition. Substitution on the triazolopyrimidine ring has the greatest impact on the approximate rates of soil decomposition as measured in a greenhouse sunflower bioassay. The data in Table II illustrate the relative rates of soil decomposition of a series of alkyl, haloalkyl and halo substituted triazolopyrimidines. Approximate soil half-lives range from 13 days for the unsubstituted and 6-chloro substituted compounds to 171 days for the 5,7-dimethyl substituted material. Table III list the approximate soil half-lives for a series of alkoxy substituted compounds and two reference alkyl substituted and one reference haloalkyl substituted materials. All of the alkoxy substituted compounds have approximately equal or shorter soil half-lives by comparison.

In sharp contrast to the effect of heterocyclic substitution, variations in substitution on the phenyl ring of the triazolopyrimidine sulfonanilides have little impact on rates of soil decomposition. The approximate soil half-lives for a series of analogs listed in Table IV illustrates this point. The variation in soil half-lives range from 21-31 days. One exception to this point is illustrated in Table V. Incorporation of ester functionality lowers the approximate soil half-life in comparison to several closely related analogs.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

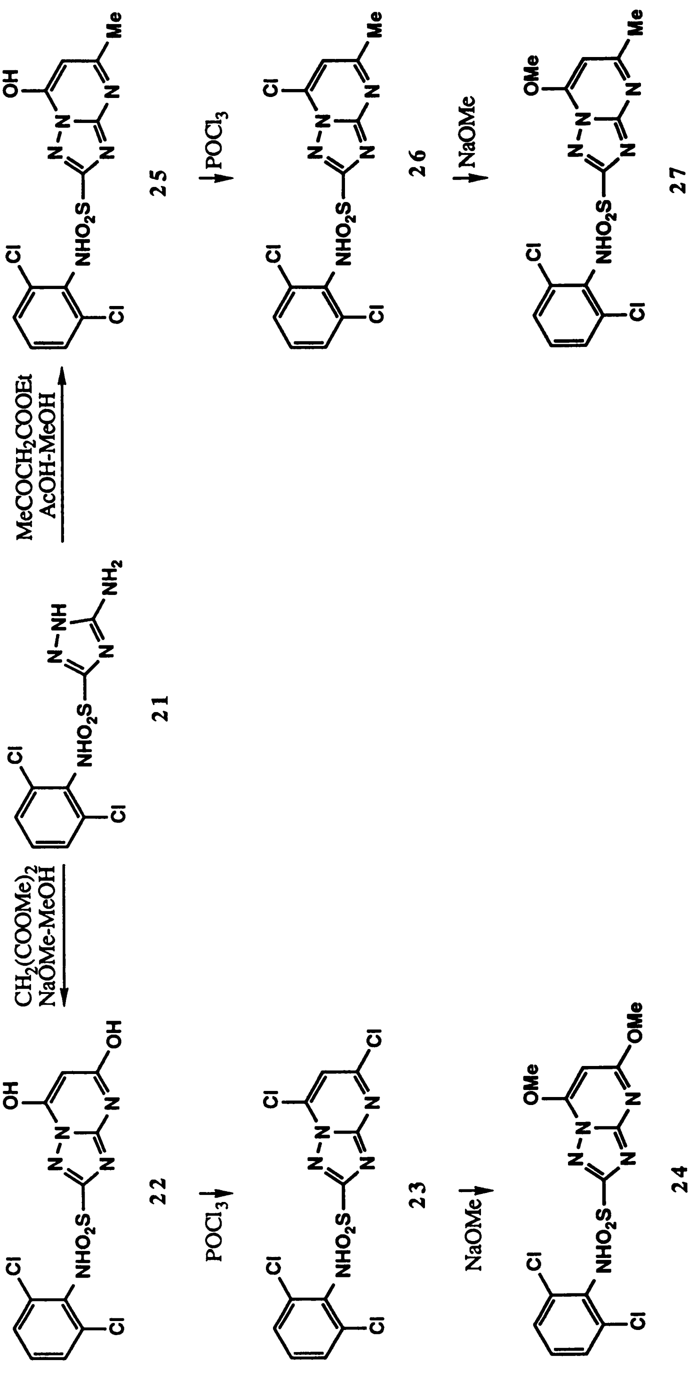
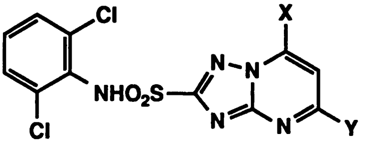

CH2(COOMe)2
NaOMe-MeOH
MeCOCH2COOEt
AcOH-MeOH
POCl3
NaOMe
21
22
23
24
25
26
27
Cl
NHO2S
N-N
N-NH
NH2
N
OH
OMe
Me

Figure 7. Synthesis of triazolopyrimidine sulfonanilides from 3-amino-1,2,4-triazole-5-sulfonanilides.

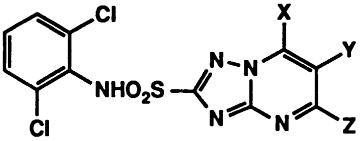
Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

Table I. *In vivo* and *in vitro* activity of a series of triazolopyrimidine sulfonanilides



X	Y	GR_{50} (ppm)	I_{50} (µM)
OEt	Me	0.8	0.0006
OMe	Me	1	0.0011
OMe	OMe	1.5	0.0028
OMe	CH_2F	2.5	0.0010
Me	Me	3	0.060
H	Me	5	0.11

Table II. Approximate soil half-lives for a series of alkyl, haloalkyl and halo substituted triazolopyrimidine sulfonanilides

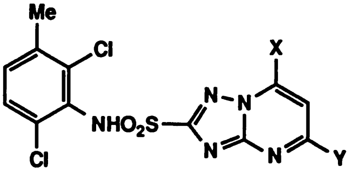


X	Y	Z	Approximate Soil Half-Life (Days)*
H	H	Me	82
Me	H	Me	171
H	Me	H	27
Me	H	H	13
H	Cl	H	11
CF_3	H	Me	44
H	H	H	13
Me	Me	Me	113
H	Me	Me	83
Me	Cl	Me	56

* Greenhouse sunflower bioassay, sandy loam soil (1% OM, pH 7.2)

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

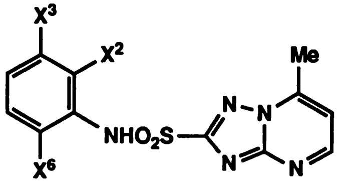
Table III. Approximate soil half-lives for a series of alkyl, haloalkyl and alkoxy substituted triazolopyrimidine sulfonanilides



X	Y	Approximate Soil Half-Life (days)*
Me	Me	181
H	Me	79
CF_3	Me	55
OMe	Me	57
OEt	Me	47
OMe	OMe	9
OEt	CH_2F	23

* Greenhouse sunflower bioassay, sandy loam soil (1% OM, pH 7.2)

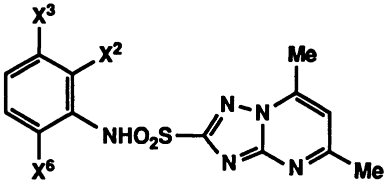
Table IV. Approximate soil half-lives for a series triazolopyrimidine sulfonanilides substituted on the phenyl ring



X^2	X^6	X^3	Approximate Soil Half-Life (days)*
Cl	Cl	H	31
Cl	Me	H	29
Cl	Cl	Me	31
CF_3	H	H	31
NO_2	Me	H	23
Cl	F	H	21

* Greenhouse sunflower bioassay, sandy loam soil (1% OM, pH 7.2)

Table V. Approximate soil half-lives for a series triazolopyrimidine sulfonanilides substituted on the phenyl ring



X^2	X^6	X^3	Approximate Soil Half-Life (days)*
Cl	Cl	H	171
Cl	Me	H	108
Cl	Cl	Me	181
COOMe	Cl	H	57

* Greenhouse sunflower bioassay, sandy loam soil (1% OM, pH 7.2)

Conclusion

The data presented here indicate that alkoxy substitution on the triazolopyrimidine ring in **1** offers opportunity for enhancing *in vitro* and *in vivo* activity. In addition alkoxy substitition provides a means to modulate the soil behavior of the triazolopyrimidine sulfonanilides.

Literature Cited

1. Kleschick, W. A.; Gerwick, B. C., In *Prospects for Amino Acid Biosynthesis Inhibitors in Crop Protection and Pharmaceutical Chemistry,* Copping, L. G.; Dodge, A. D.; Dalziel, J., Eds.; British Crop Protection Council Monograph No. 42, Lavenham Press Limited: Lavenham, Suffolk, 1989, p. 139-146.
2. Kleschick, W. A.; Costales, M. J.; Dunbar, J. E.; Meikle, R. W.; Monte, W. T.; Pearson, N. R.; Snider, S. W.; Vinogradoff, S. W. *Pestic. Sci.* **1990,** *29,* 341-355.
3. Gerwick, B. C.; Subramanian, M. V.; Loney-Gallant, V. I.; Chandler, D. P. *Pestic. Sci.* **1990,** *29,* 357-364.
4. McKendry, L. H. U.S. Patent 4,910,306 (1990).
5. Monte, W. T. U.S. Patent 4,734,123 (1988).
6. Little, J. C.; Costales, M. J.; Shankar, R. B.; Pews, R. G.; Mariam, K. G.; Thompson, S. D. European Patent Application 375,060 (1990).
7. Little, J. C.; Thibos, P. A.; Mariam, K. G.; Thompson, S. D. European Patent Application 375,061 (1990).

RECEIVED June 30, 1992

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch003

Downloaded by OHIO STATE UNIV LIBRARIES on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch004

Chapter 4

N-(Substituted-2-fluorophenyl)- and *N*-(Substituted-2-trifluoromethylphenyl)-1,2,4-triazolo-[1,5-*a*]pyrimidine-2-sulfonanilides

Synthesis and Herbicidal Activity

Mark J. Costales[1], William A. Kleschick[2], and B. Clifford Gerwick[2]

[1]Discovery Research, DowElanco Research Laboratories, P.O. Box 9002,
Walnut Creek, CA 94598
[2]Discovery Research, DowElanco Research Laboratories, P.O. Box 708,
Greenfield, IN 46140

A series of novel 2-fluoro and 2-trifluoromethyl-6-substituted anilines were prepared in a regiospecific manner and reacted with substituted 1,2,4-triazolo[1,5a]pyrimidine-2-sulfonyl chlorides to prepare the title compounds which were evaluated as potential herbicides. Heteroatom directed ortho-lithiation was used to prepare the key aniline intermediates. Details of the synthesis, biological properties and a brief discussion of the structure-activity relationship are presented.

The investigation of a series of 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonanilides (*1,2*) which exhibit herbicidal activity based on the inhibition of acetolactate synthase (ALS) (*3,4*), led to the discovery of DE-498 (Figure 1.). This compound is effective in controlling a wide variety of broadleaf and grass weed species while maintaining high levels of selectivity to agronomically important crop species such as corn, soybean and wheat. Initial structure-activity studies suggested that an in depth investigation of variously substituted 2-fluoro and 2-trifluoromethylphenyl sulfonanilides would be a promising area to investigate. A set of eighteen compounds were selected for this investigation.

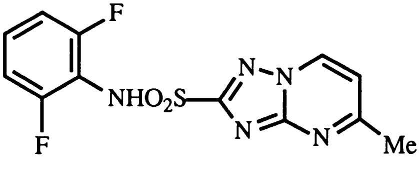


Figure 1. DE-498.

Synthesis

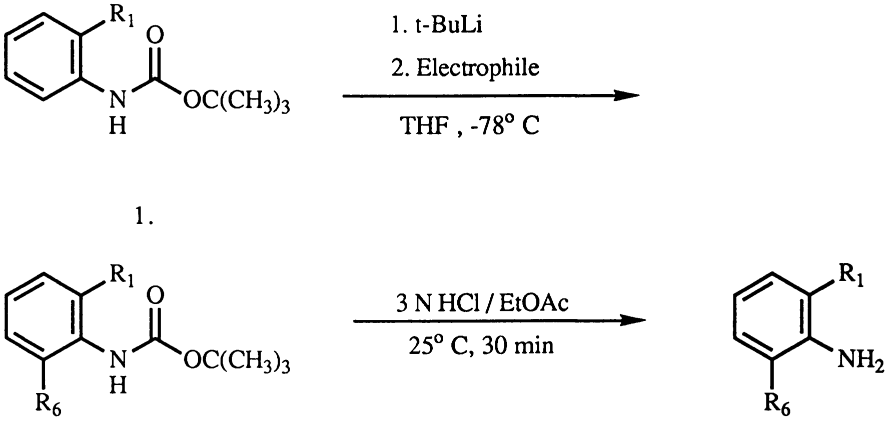
Only one aniline precursor, 2,6-difluoroaniline, was commercially available at the time of this study. Three other compounds, 2-fluoro-6-nitroaniline (*5*), 2-cyano-6-fluoroaniline (*6*) and 2-methylthio-methyl-6-trifluoromethylaniline (*7*) were available through literature procedures. The remaining compounds were prepared using slight variations of one synthetic technique, directed ortho-lithiation (*8,9*).

0097–6156/92/0504–0026$06.00/0

Downloaded by OHIO STATE UNIV LIBRARIES on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch004

The first method employed (Figure 2.) was to take an appropriate aniline precursor, protect the amine functionality as the N-(t-butoxycarbonyl)aniline (**1**), form the dianion with an excess of t-butyllithium at low temperatures and then quench the reaction mixture with the appropriate electrophile to produce the desired 2,6-disubstituted phenyl carbamate (**2**). Simple acid hydrolysis gave the desired anilines (**3**) in moderate to good yield (Table I.).

Optimization of the reaction conditions demonstrated that only a slight excess of t-butyllithium (2.1 eqs.) was necessary to achieve the highest yields and maintain regiochemical specificity. The reaction had to be carried out below $-70^{o}C$ or a rapid and exothermic decomposition of the starting material was observed. Benzyne formation is the probable cause of this decomposition in the fluorine substituted materials, however the decomposition of the trifluoromethylated compounds is not completely understood.



2. 3.

Figure 2. Preparation of 2,6-disubstituted anilines from 2-substituted anilines.

Table I.Variation of yield based on Substituents of Anilines

Compound	R_1	R_6	% Yield
3a	F	SCH_3	91
3b	F	COOH	44
3c	F	CH_3	73
3d	CF_3	CH_3	81
3e	F	CH_2CH_3	30

An other approach (Figure 3.) to the desired anilines is to react 1-fluoro or 1-trifluoromethyl-2,3 or 3-substituted benzenes (**4**) with n-butyllithium at or below $-78^{o}C$ and then quench this reaction mixture with CO_2. The resulting benzoic acids (**5**) are then converted to benzamides (**6**) and finally using standard Hoffman conditions to the aniline (**7**). The reaction must be carried out at or slightly below $-78^{o}C$ because as in the previous sequence a rapid, exothermic decomposition of

Downloaded by OHIO STATE UNIV LIBRARIES on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch004

reactants takes place at or near -65°C. In addition at temperatures above -78°C more than one regioisomer is formed during the initial lithiation reaction. For example, the reaction of 3-methoxybenzotrifluoride (**4e**) with n-butyl lithium at -70°C, upon quenching with CO_2, gives two isomeric benzoic acids in an overall 70% yield. The ratio of isomers is 7 to 3 with the major product being 2-methoxy-6-trifluoromethylaniline (**7e**). The minor component was identified by NMR to be 2-methoxy-4-trifluoromethylaniline. The number and structure of isomers formed during these reactions varies with the starting material, but in all cases formation of unwanted isomers was eliminated by careful control of the reaction temperature. Decreasing the reaction temperature much below -78°C leads to undesirably long reaction times to form the lithiated species and lower yields (Table II.).

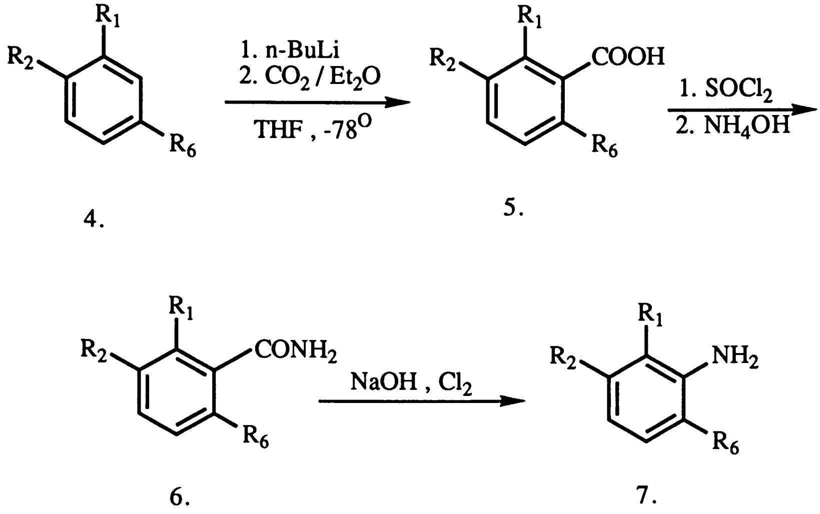


Figure 3. Preparation of 2,6 or 2,3,6-Substituted Anilines from 1,3 or 1,2,4-Substituted Benzenes.

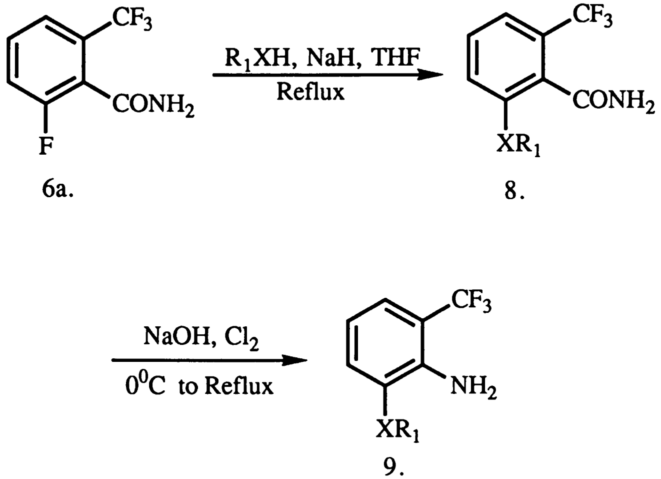
Table II. Variation of Yields Based on Benzene Substitution

Compound	R_1	R_2	R_6	% Yield (overall)
7a	CF_3	H	F	45
7b	F	H	OCH_3	52
7c	F	OCH_3	F	32
7d	F	CH_3	F	47
7e	CF_3	H	OCH_3	55

The remaining target anilines are prepared using 2-fluoro-6-trifluoromethylbenzamide (**6a**) as the starting material (Figure 4.). Otherwise unobtainable alkoxy and alkylamino substituents were prepared by deprotonation of the appropriate alcohol or amine with sodium hydride in THF and displacement of the fluorine from the

Downloaded by OHIO STATE UNIV LIBRARIES on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch004

starting benzamide to give 6-alkoxy or 6-alkylaminobenzamides (**8**). These compounds are then converted to the desired amines (Table III.) (**9**).



6a. 8. 9.

Figure 4. Preparation of Alkoxy and Alkylamino Anilines.

Table III. Variation in Yield of Alkoxy and Alkylaminoanilines

R_1XH	% Yield
CH_3CH_2OH	45
CF_3CH_2OH	31
$(CH_3)_2CHOH$	63
$(CH_3)_2NH$	71

The preparation of the desired sulfonanilides (**13**) is accomplished by the reaction of 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride (**12**) with the appropriate aniline (Figure 5). The preparation of sulfonyl chloride (**12**) is accomplished by reacting the aminotriazole (**10**) with acetoacetaldehyde dimethylacetal to give the intermediate 2-benzylthio-5-methyl-1,2,4-triazolo[1,5-a]- pyrimidine (**11**) in 74% yield. Reaction of this thioether with chlorine in aqueous media (e.g. aqueous acetic acid or hydrochloric acid) produces the desired sulfonyl chloride (**12**) in 90% yield. This sulfonyl chloride is quite stable at room temperature when anhydrous and may be stored for many months. To one equivalent of aniline dissolved in a suitable polar, aprotic solvent (e.g. acetonitrile) one adds an equivalent of sulfonyl chloride (**12**) and an excess of pyridine. When the reaction is complete the solvent is removed and the residue is washed with H_2O and then ether. The solid is filtered and dissolved in 1N NaOH. This solution is washed with CH_2Cl_2 and the pH of the aqueous phase adjusted with 1N HCl, to near pH 5, to precipitate the desired sulfonanilide (**13**) in moderate to good yield (40-90%).

Downloaded by OHIO STATE UNIV LIBRARIES on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch004

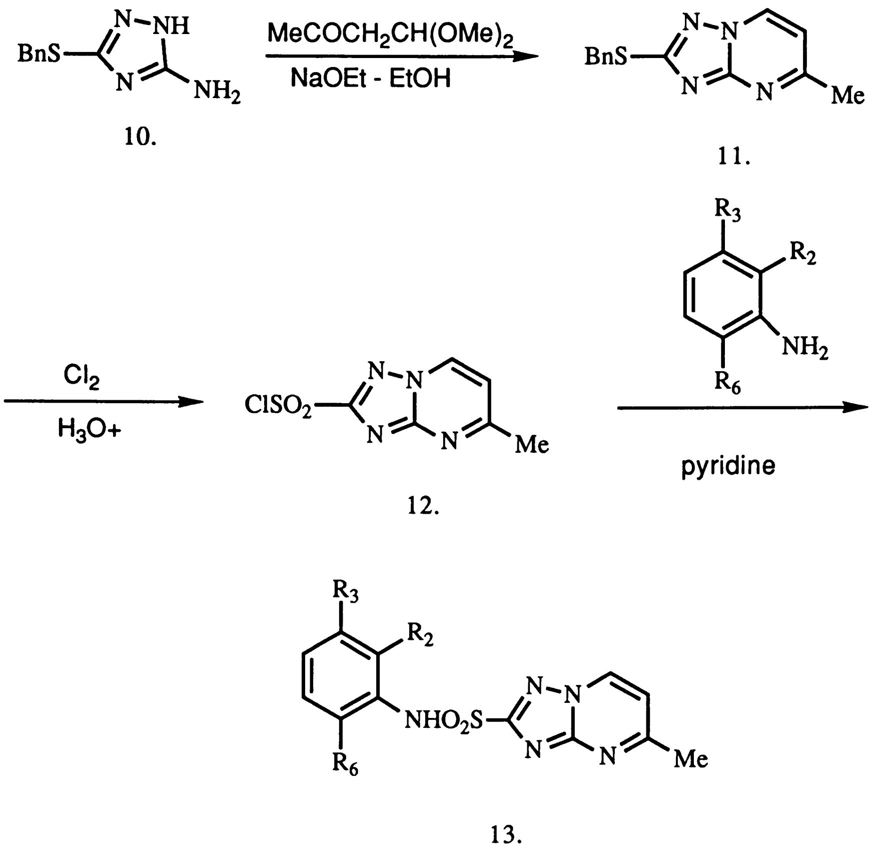


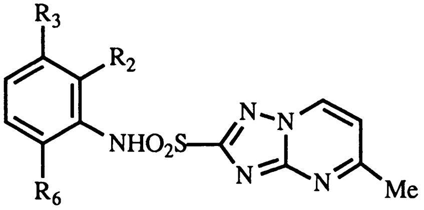
Figure 5. Preparation of 5-methyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonyl chloride and 1,2,4-triazolo[1,5-a]pyrimidine-2-sulfonanilides.

Results and Discussion

The biological activity of the previously described sulfonanilides was determined and is summarized in Table IV. In general these compounds are more efficatious on broadleaf species than on grass or sedeg species. The *in vivo* herbicidal activity was determined on eight broadleaf weed species, *Xanthium strumarium, Datura strumarium, Chenopodium album, Ipomoea hederacea, Amaranthus retroflexus, Abutilon theophrasti, Veronica persica* and *Polygonum convolvulus*.. This herbicidal activity was assessed visually after 2 weeks and is expressed in terms of the log 1/GR_{80}. The GR_{80} is the concentration of sulfonanilide necessary to cause an average growth reduction of 80% on all the target species as compared to the growth of untreated plants. The *in vitro* biological activity is determined on acetolactate synthase (ALS, EC 4.1.3.18). This activity is expressed as the log 1/I_{50}. The I_{50} is the concentration of sulfonanilide required to eliminate 50% of the enzymes ability to catalyse the conversion of pyruvate to a-acetolactate or the conversion of a-ketobutyrate to a-aceto-a-hydroxy-butyrate in the biosynthesis of leucine, isoleucine and valine in plants. Crop selectivity was estimated by the growth reduction of *glycine max* (soybeans).

This growth reduction is expressed in terms of $1/GR_{20}$. The GR_{20} is the concentration of sulfonanilide necessary to cause a 20% growth reduction on soybeans as compared to the growth of untreated plants.The highlighted data represents the values obtained for DE-498 and are used as standards for comparison.

Table IV. Comparison of *in vivo* and *in vitro* Biological Activity of 1,2,4-Triazolo[1,5-a]pyrimidine-2-sulfonanilides



R_2	R_3	R_6	-Log $1/GR_{80}$ (PPM)	Log $1/I_{50}$ (μM)	-Log $1/GR_{20}$ (μM)
CF_3	H	OCH_3	0.59	2.50	0.25
CF_3	H	OCH_2CF_3	0.79	1.48	0.31
CF_3	H	OCH_2CH_3	0.85	1.08	1.00
CF_3	H	CH_3	1.07	0.87	1.21
F	CH_3	F	1.13	1.39	1.15
F	H	$COOCH_3$	1.28	0.80	1.95
F	H	F	1.47	0.71	2.13
F	H	SCH_3	1.56	0.65	1.78
F	H	COO(i-Pr)	1.68	0.54	1.20
F	H	COOEt	1.70	0.52	1.61
F	H	Cl	1.71	0.47	0.46
F	H	CF_3	1.98	-1.33	1.25
F	H	CH_2CH_3	2.10	0.92	1.89
F	H	OCH_3	2.11	-0.37	2.00
F	H	CN	2.40	-0.62	2.55
F	H	CH_3	2.45	0.16	2.76
F	H	NO_2	2.70	-0.58	2.25
CF_3	H	CH_2SCH_3	2.88	-1.21	2.88
F	OCH_3	F	3.00	1.10	3.00

Several analogues show higher levels of both *in vivo* and *in vitro* activity than DE-498. In addition several compounds have *in vitro* biological activity greater than DE-498, but, they exhibit lower *in vivo* control than the standard. These differences are due, most probably, to a combination of effects. Inefficient uptake by the plant or poor translocation in the plant may be the cause. However, physical property measurements indicate that all of these molecules have very similar log P and pKa values. This indicates that uptake and translocation should be similar throughout the series. Metabolic detoxification must also play a role in this apparent discrepancy.

Downloaded by OHIO STATE UNIV LIBRARIES on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch004

Downloaded by OHIO STATE UNIV LIBRARIES on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch004

In all cases crop selectivity was less for the new analogues than for DE-498. Crop selectivity and weed species insensitivity have been shown to result from metabolism of the 1,2,4-triazolo[1,5-a]pyrimidine portion of the molecule. However, detailed metabolic studies (*10*) have not been performed on this series with the exception of DE-498 (Figure 6.). These studies indicate that hydroxylation of the methyl group of DE-498 to produce the 5-hydroxymethyl triazolopyrimidine (**14**) is the major path of detoxification in corn and non-sensitive weeds. Another metabolite, which is not fully characterized, is the major product of detoxification in soybeans. Inhibition of this detoxification or an altering of the rate at which it proceeds are the most probable cause of the decrease in crop selectivity.

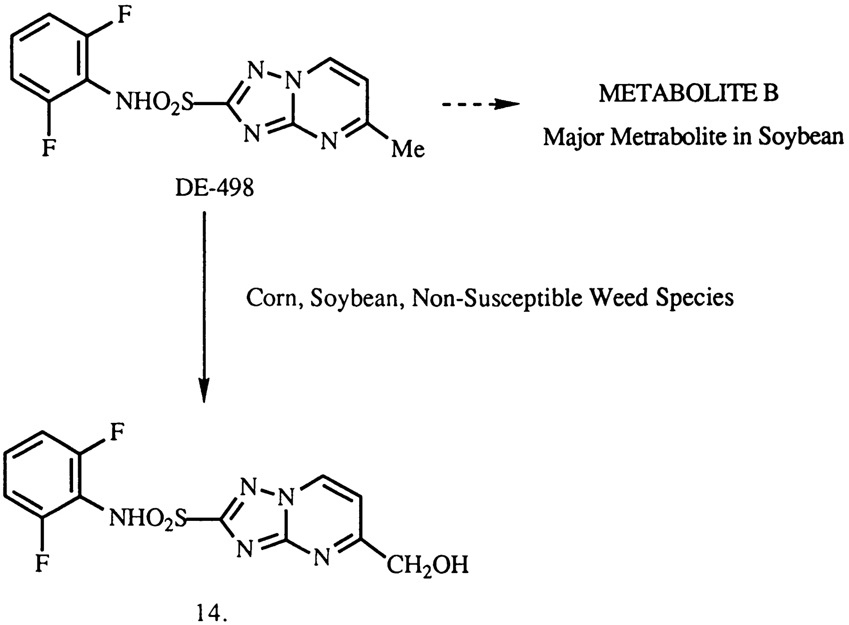

F
NHO2S
N
N
N
N
Me
F
DE-498
METABOLITE B
Major Metrabolite in Soybean
Corn, Soybean, Non-Susceptible Weed Species
F
NHO2S
N
N
N
N
CH2OH
F
14.

Figure 6. Metabolism of DE-498 in Plants.

Conclusion

The data presented here indicates that DE-498 has the most effective combination of herbicidal activity and crop selectivity of a series of N-(substituted-2-fluorophenyl) and N-(substituted-2-trifluoromethylphenyl)-1,2,4-triazolo[1,5-a]-pyrimidine-2-sulfonanilides prepared for this study.

Acknowledgment

I would like to thank Virginia Miner for her expertise in nuclear magnetic resonance which was necessary to determine the correct structures of the various intermediates and Eric Martin and co-workers for the measurement of physical properties of these sulfonanilides.

Literature Cited

1. Kleschick, W. A. ; Costales, M. J. ; Gerwick, B. C. ; Holtwick, J. B. ; Meikle, R. W. ; Monte, W.T.; Pearson, N. R. ; Snider, S. W. ; Subramanian, M. V. ;VanHeertum, J. C. and Vinogradoff, A. P. preceding chapter in this volume.
2. Kleschick, W. A. ; Costales, M. J. ; Dunbar, J. E. ; Meikle, R. W. ; Monte, W.T.; Pearson, N. R. ; Snider S. W. and Vinogradoff, A. P. *Pestic. Sci* , 1990, 29, 341-355.
3. Gerwick, B. C. ; Subramanian, M. V. ; Loney-Gallant, V. I. ;Chandler, D. P. *Pestic. Sci.* 1990, 29, 357-364.
4. Stidham, Mark A. *Weed Science*, 1991, 39, 428-434.
5. Kavalek, J. et al.; *Coll. Advan. Chem. Technol.* , Pardubice, Czech, 1967, No. 16 (Pt. 2), 9.
6. Gray, J. ;Waring D. R. *J. Het. Chem.* ; 1980, 17, 65.
7. Chupp, J. P. et al. *J. Org. Chem.*, 1984.
8. Muchowski, J. M. ; Venuti, M. C. *J. Org. Chem,* 1980, 45, 4798-4801.
9. Burton, R. A. ; Roe, A. M. Brit. Patent 1,080,167, 1968; *Chem. Abstr.* 1968, 68, 95518r.
10. Swisher, B. A. ; Gerwick, B. C. ; Cheng, M. ; Miner, V. W. ; deBoer, G. J. *Abstr. Meet. Weed Sci. Soc. Am.* 1991, 31, 50.

RECEIVED June 30, 1992

Downloaded by OHIO STATE UNIV LIBRARIES on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch004

Chapter 5

New Pyrazole Sulfonylureas

Synthesis and Herbicidal Activity

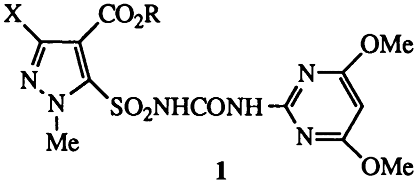
S. Yamamoto[1], T. Sato[1], K. Morimoto[1], and T. Nawamaki[2]

[1]Central Research Institute, Nissan Chemical Industries, Ltd., Tsuboi-cho 722, Funabashi, Chiba 274, Japan
[2]Research Station of Biological Science, Nissan Chemical Industries, Ltd., Shiraoka 1470, Saitama 349–02, Japan

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

A number of 3-substituted pyrazole-5-sulfonamides were prepared by various methods that included diazotization, lithiation, cyclization and chlorination. These sulfonamides were converted into 3-substituted pyrazole-5-sulfonylureas that possessed high herbicidal activity. Among them, NC-319: methyl 3-chloro-5-(4,6-dimethoxypyrimidin-2-ylcarbamoylsulfamoyl)-1-methylpyrazole-4-carboxylate is found to be a potent herbicide against broad-leaf weeds and sedges in corn at both pre- and post-emergence applications. This chapter reviews the synthesis and the herbicidal activity of NC-319 and its related compounds.

Sulfonylurea herbicides are a class of compounds having extremely low rates at pre- and post-emergence applications (*1-3*). We were interested in their structures and herbicidal activity and attempted to find new compounds with both high activity and excellent crop safety. In our previous study (*4*), it was found that sulfonylurea compounds having pyrazole moieties (pyrazolesulfonylureas) possessed high herbicidal activity and several compounds, in which the sulfonylurea bridge was bound to the 5-position of the pyrazole ring (pyrazole-5-sulfonylureas **1**), had high herbicidal activity against paddy weeds without phytotoxicity to rice plants. Among them, pyrazosulfuron-ethyl **1b** is a prominent herbicide used in paddy fields and is commercialized mainly in Japan, Korea and China by Nissan Chemical Industries. In our continuing study of the structure-activity relationships of pyrazole-5-sulfonylureas **1**, we introduced various substituents into the 3-position on the pyrazole ring of **1** in the hope of finding a new herbicide which could be used for upland crops.



1

1a; X=Cl, R=Me (NC-319)
1b; X=H, R=Et (pyrazosulfron-ethyl)

0097–6156/92/0504–0034$06.00/0

Synthesis

Three coupling reactions between pyrazole and pyrimidine moieties are shown in Figure 1. Pyrazole-5-sulfonylureas **1** were synthesized by the reactions of pyrazole-5-sulfonylisocyanates **3** or pyrazole-5-sulfonylcarbamates **4**, prepared from pyrazole-5-sulfonamides **2**, with 2-amino-4,6-dimethoxypyrimidine **5** (*5, 6*). The condensation of phenyl pyrimidinylcarbamate **6** with **2** in the presence of DBU also afforded **1** (*7*).

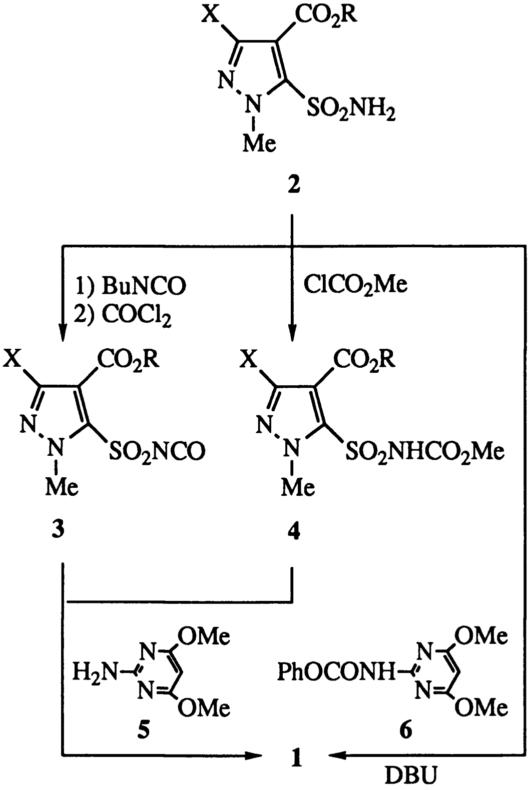


Figure 1. Synthetic Routes of Pyrazole-5-sulfonylureas

Therefore, we concentrated on finding new synthetic methods for pyrazole-5-sulfonamides **2**, the key intermediates for our program. Since little had been known about the synthesis of **2** containing a carboxylate group, which was indispensable for satisfactory herbicidal activity of **1**, we developed the following four methods.

Diazotization Method. Pyrazole-5-sulfonamides **2** were prepared from 5-aminopyrazoles **7** by two diazotization methods (Figure 2) (*8*). Hydrochloric acid salts of **7** were diazotized in dilute sulfuric acid followed by decomposition with sulfur dioxide and cuprous chloride in acetic acid to obtain pyrazole-5-sulfonylchlorides **8**. They were aminated with ammonia to obtain **2**. Unless equimolecular quantities of hydrochloric acid and **7** were used in this diazotization reaction, yields of **8** decreased and 5-chloropyrazoles **9** and pyrazoles **10** increased as by-products.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

5-Aminopyrazoles **7** were also diazotized in concentrated hydrochloric acid followed by decomposition with sulfur dioxide coupled with a trace of cuprous chloride in carbon tetrachloride to obtain **9** in the place of **8**. In cases that the 3-position of pyrazole ring of **7** were hydrogen atoms, we were surprised to find that its diazonium salts decomposed with sulfur dioxide in the absence of copper catalysts to give **9** in good yields (*9*). The chlorine atoms of **9** were substituted into mercapto groups with sodium hydrosulfide in DMF. Subsequent oxidative chlorination and amination gave **2** in good yields.

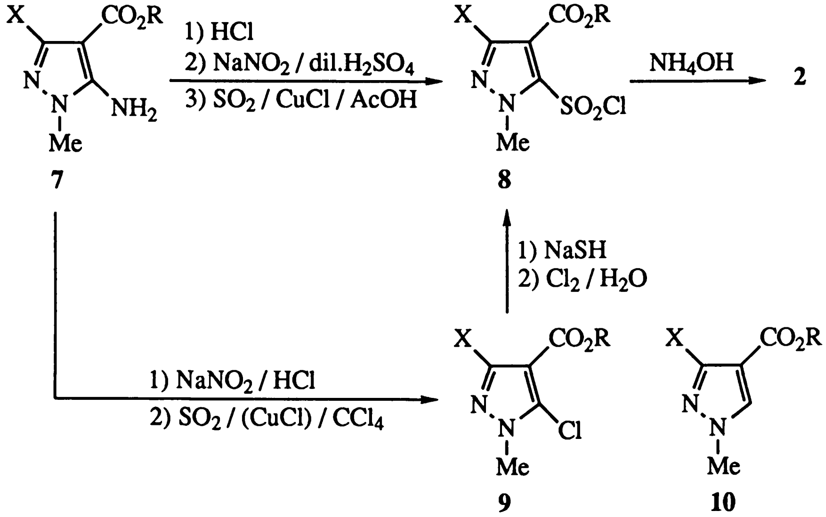


Figure 2. Synthesis of Pyrazole-5-sulfonamides *via* Diazotization Method

Figure 3 shows an application of the diazotization method for **2a**: the sulfonamide of NC-319 (*10, 11*). Diaminopyrazole derivative **11** (*12*), prepared from trichloroacetonitrile, methyl cyanoacetate and hydrazine, was diazotized in concentrated hydrochloric acid and decomposed with cuprous chloride to obtain 3,5-dichloropyrazole derivative **12**. This dediazotization required significant quantity of cuprous chloride to decompose the diazonium group on the 3-position of the pyrazole ring. After methylation of **12**, 3,5-dichloropyrazole derivative **13** was reacted with sodium hydrosulfide in DMF to obtain 3-chloro-5-mercaptopyrazole derivative **14** in good yield. Since the chlorine atom on the 3-position of **13** was stable enough to remain intact under basic conditions, we could succeed in regioselective preparation of **14**. The mercaptopyrazole **14** was converted to **2a** by the ordinary method. In cases that the 5-aminopyrazoles **7** were readily prepared as starting materials, the diazotization methods afforded very useful routes for the synthesis of **2**.

Lithiation Method. Figure 4 shows the preparation of pyrazole-5-sulfonamides **2** *via* lithiation method (Yamamoto, S. *et al. J. Heterocyclic Chem.*, in press.). Pyrazoles **10** were lithiated at the 5-position with LDA in THF at -60°C, and sulfur dioxide was bubbled into the solution of lithiated pyrazoles **20** to obtain lithium sulfinates **21**. Subsequently, **21** were chlorinated with N-chlorosuccinimide (NCS) and aminated with ammonia to give pyrazole-5-sulfonamides **2**. This method was the most useful one for our program. Because it had become feasible to introduce a wide range of substituents into the 3-position on the pyrazole ring of **2**.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

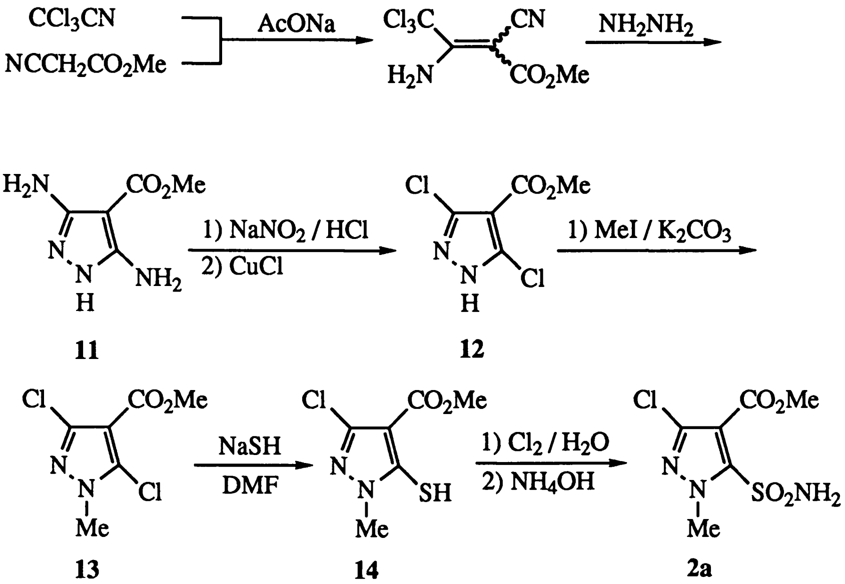

CCl3CN
NCCH2CO2Me
AcONa
Cl3C
CN
H2N
CO2Me
NH2NH2
1) NaNO2 / HCl
2) CuCl
11
12
1) MeI / K2CO3
NaSH
DMF
13
14
1) Cl2 / H2O
2) NH4OH
2a

Figure 3. Synthesis of the Sulfonamide of NC-319 *via* Diazotization Method

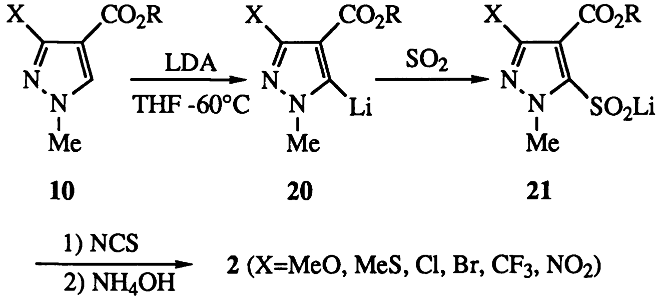

LDA
THF -60°C
SO2
10
20
21
1) NCS
2) NH4OH
2 (X=MeO, MeS, Cl, Br, CF3, NO2)

Figure 4. Synthesis of Pyrazole-5-sulfonamides *via* Lithiation Method

Cyclization Method. Synthesis of pyrazole-5-sulfonamides **2** *via* cyclization method is illustrated in Figure 5. The reaction of bisbenzylthioketenedithioacetals **15** (*13*) with methylhydrazine under heating gave 3-benzylthiopyrazoles **16'** as the major products and 5-benzylthiopyrazoles **16** as the minor. On the other hand, the reaction of 1,3-dithietanes **17** (*14*), prepared from malonates and carbon disulfide, with methylhydrazine in chloroform at room temperature afforded 3-hydroxy-5-mercaptopyrazoles **18** without the positional isomers. After benzylation of the mercapto groups of **18**, hydroxy groups of **16** were converted to methoxy and difluoromethoxy groups by carbene reactions to obtain 3-alkoxy-5-benzylthiopyrazoles **19c,d**. Oxidative chlorination and amination of **19c,d** formed **2c,d**.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

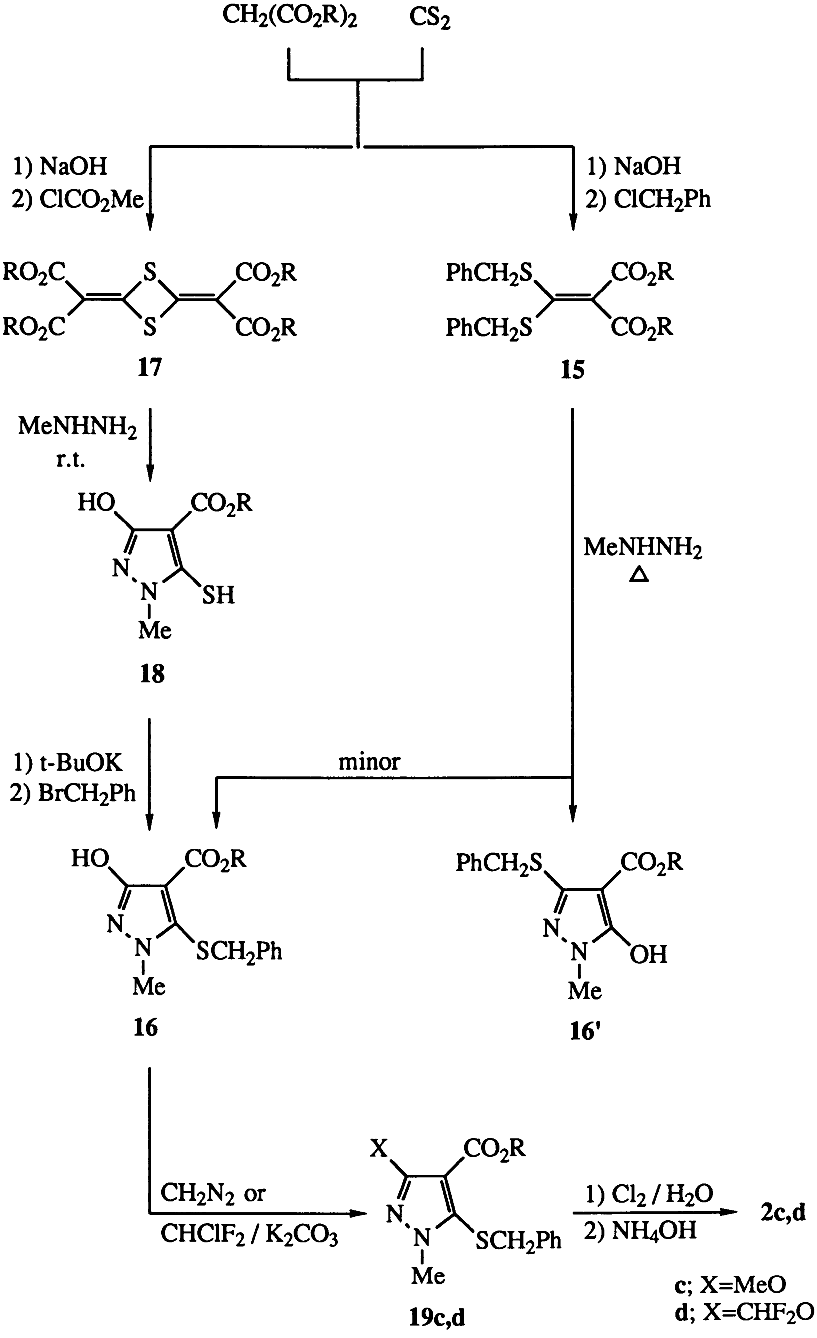

CH2(CO2R)2
CS2
1) NaOH
2) ClCO2Me
1) NaOH
2) ClCH2Ph
RO2C
S
CO2R
RO2C
S
CO2R
17
PhCH2S
CO2R
PhCH2S
CO2R
15
MeNHNH2
r.t.
HO
CO2R
N
N
SH
Me
18
MeNHNH2
Δ
1) t-BuOK
2) BrCH2Ph
minor
HO
CO2R
N
N
SCH2Ph
Me
16
PhCH2S
CO2R
N
N
OH
Me
16'
CH2N2 or
CHClF2 / K2CO3
X
CO2R
N
N
SCH2Ph
Me
19c,d
1) Cl2 / H2O
2) NH4OH
2c,d
c; X=MeO
d; X=CHF2O

Figure 5. Synthesis of Pyrazole-5-sulfonamides *via* Cyclization Method

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

Chlorination Method. We tried electrophilic chlorinations on the 5-position of pyrazoles **10**. It was found that the reaction of **10** with NCS under heating conditions without solvents afforded chloropyrazoles **9** in good yields (Figure 6). Other chlorination reagents, such as chlorine or sulfuryl chloride were not useful for this reaction. Unless this chlorination was carried out at lower than 110°C, the yields of **9** decreased and side chain chlorinated compounds **22** increased. On the other hand, the chlorination of **10** with chlorine under UV irradiation gave only **22**. Therefore, we think the chlorination with NCS (NCS chlorination) is not a radical reaction but an ionic one.

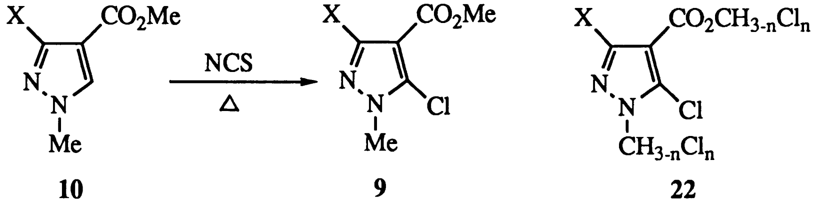


Figure 6. Chlorination of Pyrazoles with NCS

Figure 7 shows a route for the preparation of NC-319 to be used for field trials, that includes the NCS chlorination as a key step. The reaction of methyl ethoxymethylenecyanoacetate **23** with masked methylhydrazine **24** afforded 3-aminopyrazole derivative **25** (*15*), followed by Sandmeyer reaction of **25** and the NCS chlorination of **26** to give dichloropyrazole derivative **13**. By the ordinary method, **13** was converted into **1a** (NC-319) *via* sulfonamide **2a**. The procedure given here could be used conveniently to prepare quantities up to several kilograms.

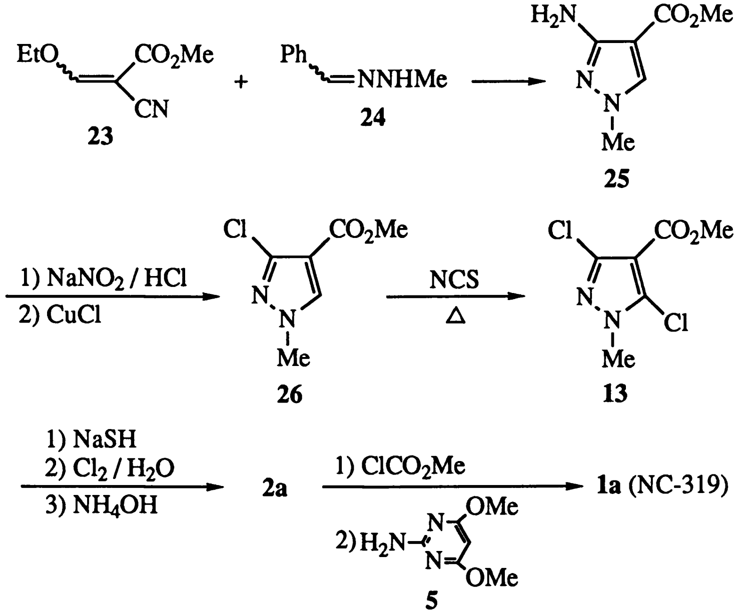
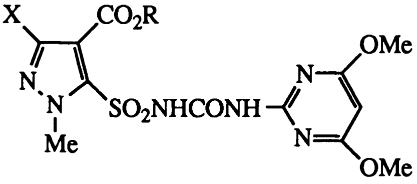


Figure 7. Synthesis of NC-319

Herbicidal Activity

The herbicidal activity and safety for corn of the 3-substituted pyrazole-5-sulfonylureas prepared on this study are summarized in Table I. This table shows the inhibition rates at post-emergence application in greenhouse condition and the dosage was 40g a.i./ha. Visual assessments rating from 0 to 9 were made at 17 days after application.

Table I. Herbicidal Activity of 3-Substituted Pyrazole-5-sulfonylureas in Greenhouse



Inhibition Rates at Post Emergence(40 g a.i./ha, 17 DAT)

X	R	Broad-leaf weeds	Sedges	Gramineous weeds	Corn
H	Me	9	9	4	8
H	Et	9	9	4	8
Me	Me	9	9	4	8
Me	Et	9	9	4	9
Cl	Me	9	9	4	0
Cl	Et	9	9	4	0
Br	Me	9	9	3	0
Br	Et	9	9	3	0
OMe	Et	9	9	6	7
$OCHF_2$	Et	6	5	0	0
SMe	Et	6	0	0	0
CF_3	Et	7	4	0	1
NO_2	Et	8	7	4	8

0 = No Injury, 9 = Completely Killed

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

In a class of the compounds that the substituents of the 3-position on pyrazole ring were hydrogen atom, methyl group, chlorine atom, bromine atom and methoxy group possessed high herbicidal activity against broad-leaf weeds and sedges. Especially, the compounds substituted with chlorine atom or bromine atom showed good selectivity for corn. Compounds with other substituents showed unsatisfactory activity. Based on both the safety for corn and the herbicidal activity against cocklebur (*xanthium strumarium*) and velvetleaf (*abutilon theophrasti*), which are troublesome weeds in corn fields, we decided to develop **1a**: methyl 3-chloro-5-(4,6-dimethoxypyrimidin-2-ylcarbamoylsulfamoyl)-1-methylpyrazole-4-carboxylate (NC-319) as a potent herbicide in corn (*6*).

Field trials were conducted in several locations in the corn belt. Table II shows the mean cocklebur and velvetleaf control rates at early post- and post-emergence applications of NC-319. The application rates were from 18 to 140 g a.i./ha and the reference herbicides were atrazine, dicamba and 2,4-D. Visual assessments were made about 25 days after applications. From the field trials, NC-319 completely controlled cocklebur and velvetleaf with the rates 18-70g a.i./ha at these timings (*16*).

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

Table II. Cocklebur and Velvetleaf Control in Corn Fields with Early Post- and Post-emergence Applications of NC-319 (U.S.A. 1990)

Mean Inhibition Rates (%, 25 DAT)

	a.i. g/ha	Early Post a) Cocklebur	Early Post a) Velvetleaf	Post b) Cocklebur	Post b) Velvetleaf
NC-319	18	98	94	87	65
	35	99	95	93	80
	70	99.5	94	95	95
	140	99	92	97	84
Atrazine	2240	87	70	95	56
Dicamba	140	100	-	96	59
2,4-D	280	100	-	-	65

a) Leaf stage of Corn; 0-4 b) Leaf stage of Corn; 4-12

Moreover, NC-319 demonstrated excellent activity against the above weeds on pre-emergence application at the rates 70-90g a.i./ha. The details of it were presented at Brighton Crop Protection Conference (1991) (*17*).

Conclusion

Four synthetic methods including diazotization, lithiation, cyclization and chlorination for the preparation of 3-substituted pyrazole-5-sulfonamides **2** were developed and they were converted to novel pyrazole-5-sulfonylurea herbicides **1**. Among them, NC-319 **1a**: methyl 3-chloro-5-(4,6-dimethoxypyrimidin-2-ylcarbamoylsulfamoyl)-1-methylpyrazole-4-carboxylate was found to be a promising herbicide against broad-leaf weeds and sedges in corn fields. At pre- and post-emergence applications, NC-319 controlled cocklebur and velvetleaf with far lower application rates than reference herbicides.

Acknowledgements

We wish to express our thanks to Dr. Mamoru Hayashi, General Manager of Central Research Institute, Nissan Chemical Industries, Ltd. and Dr. Gozyo Sakata, Manager of New Business Planning Dept., Nissan Chemical Industries, Ltd., for their continuing guidance and encouragement.

Literature Cited

1. Levitt, G.; Plog, H.L.; Weigel, R.C.; Fitzgerald, D.J. *J. Agric. Food Chem.* **1981,** 29, 416.
2. Levitt, G. In *Sulfonylureas: New High Potency Herbicides;* Miyamoto, J.; Kearney, P.C., Eds.; Pesticide Chemistry, Human Welfare and the Environment; Pergamon Press: Oxford, 1983; Vol. 1, pp 243-250.
3. Levitt, G. In *Synthesis and Chemistry of Agrochemicals II;* Baker, D.R.; Fenyes, J.G.; Moberg, W.K., Eds.; ACS Symposium Series No. 443; American Chemical Society: Washington, DC, 1991; pp 16-31.
4. Yamamoto, S.; Sato, T.; Iwasawa, Y.; Suzuki, F.; Ikai, T.; Suzuki, K.; Nawamaki, T. *J. Pesticide Sci.* **1990**, 15, 531.
5. Suzuki, F.; Iwasawa, Y.; Sato, T.; Ikai, T.; Oguti, T., Eur. Patent 87,780, 1983.
6. Yamamoto, S.; Sato, T.; Ikai, T.; Oguti, T.; Nawamaki, T., U.S. Patent 4,668,277, 1987.
7. Morimoto, K.; Makino, K.; Yamamoto, S.; Sakata, G. *J. Heterocyclic Chem.***1990**, 27, 807.

8. Sato, T.; Morimoto, K.; Yamamoto, S. *Proc. 53th Symposium on Organic Synthesis, Japan* **1988**, 17.
9. Morimoto, K.; Sato, T.; Oya, E.; Yamamoto, S., Japan Kokai Tokkyo Koho 61-100,570, 1986; *Chem. Abstr.* **1986**, 105, 226553f.
10. Sato, T.; Morimoto, K.; Yamamoto, S., Japan Kokai Tokkyo Koho 62-4271, 1987; *Chem. Abstr.* **1987**, 107, 77793w.
11. Sato, T.; Morimoto, K.; Yamamoto, S., Japan Kokai Tokkyo Koho 62-4272, 1987; *Chem. Abstr.* **1987**, 107, 39807w.
12. Spasova, M.; Zakharieva, R.; Golovinski, E. *Z. Chem.* **1980**, 20, 95; *Chem. Abstr.* **1980**, 93, 95181s.
13. Gompper, R.; Toepfl, W. *Chemische Berichte* **1962**, 95, 2861.
14. Raasch, M. S. *Chem. Comm.* **1966**, 16, 577.
15. Druey, J; Schmidt, P., U.S. Patent 3,399,196, 1968.
16. Ito, T.; Suzuki, K.; Nawamaki, T.; Watanabe, S.; Yamamoto, S.; Morimoto, K. *Proc. North Central Weed Science Society* **1990**, 45, 35.
17. Suzuki, K.; Nawamaki, T.; Watanabe, S.; Yamamoto, S.; Sato, T.; Morimoto, K.; Wells, B.H. *Proc. Brighton Crop Protection Conference* **1991**, 1, 31.

RECEIVED March 13, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch005

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Chapter 6

Synthesis and Quantitative Structure–Activity Relationships of Pyridylsulfonylurea Herbicides

S. Murai, Y. Nakamura, T. Akagi, N. Sakashita, and T. Haga

Central Research Institute, Ishihara Sangyo Kaisha, Ltd., 2–3–1, Nishi-shibukawa, Kusatsu, Shiga 525, Japan

SL-950 (Nicosulfuron, ISO proposed) is a post emergence application herbicide for corn which has a novel type of pyridylsulfonylurea structure. The analogs of SL-950 were synthesized, and their quantitative structure activity relationship analyses was carried out to understand the drug-receptor interaction. The QSAR equations obtained indicates SL-950 is the most effective compound among those examined.

SL-950 is a pyridylsulfonylurea type herbicide for corn which has N,N-dimethylcarbamoyl group at the 3-position on pyridine ring (compound **19** in Table I) and shows a broad herbicidal spectrum against both grasses and broadleaf weeds (*1*).

For the purpose of studying the structure activity relationships of these pyridylsulfonylurea compounds, we prepared 55 analogs of SL-950, each of which bears different substituents R^1, R^2, R^3, X^1, X^2 and Z as shown in Table I. In this paper substituents R^3 on the 6-position of the pyridine ring were the only pyridine substitutions examined. It was clear from a previous study that the introduction of substituents into any position except 6-position of pyridine ring of pyridylsulfonylurea remarkably decreased the herbicidal activity (*1*).

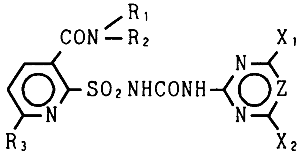
Synthesis

Synthetic methods of sulfonamide precursors for sulfonylureas are summarized in Scheme I (*2*). Physico-chemical properties of these sulfonamides and sulfonylureas are shown in reference (*3*). Sulfonamide intermediates for compounds **1**～**35** without any substituent at the 6-position on pyridine ring were prepared by route A in scheme I, while precursors for compounds **36**～**56** which have a certain substituent R^3 at 6-position were prepared by route either B, C or D. In route B, 2,6-dichloronicotinamides,

0097–6156/92/0504–0043$06.00/0

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Table I Synthesized SL-950 Analogs



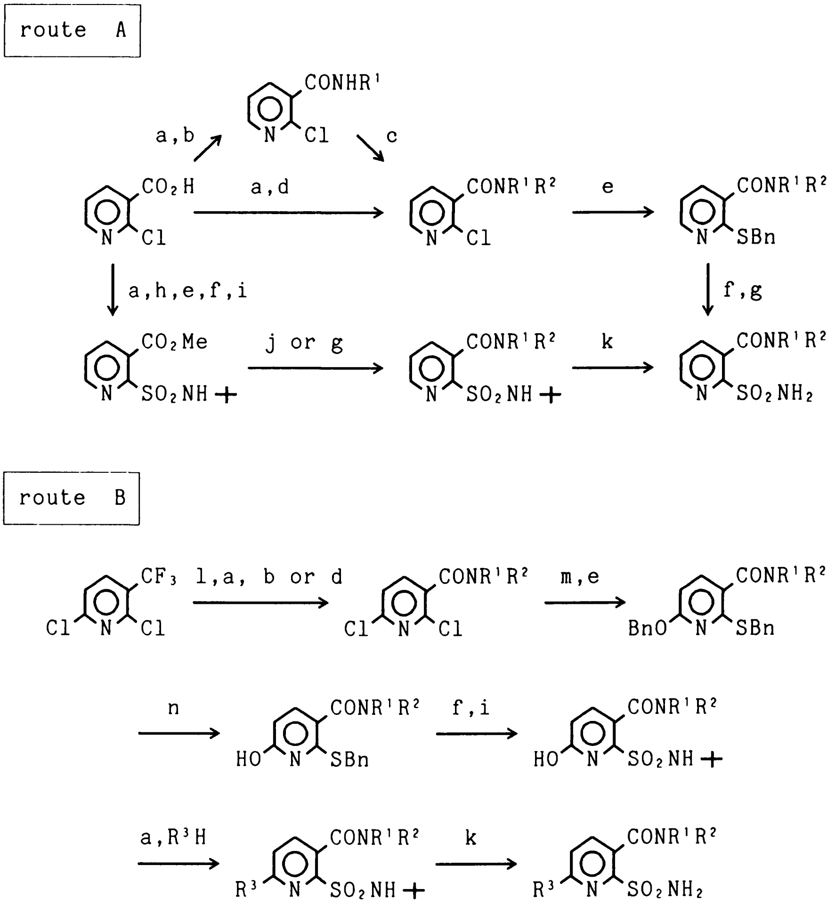
Compd.	R¹	R²	R³	X¹	X²	Z
1	H	H	H	OCH_3	OCH_3	CH
2	CH_3	H	H	CH_3	CH_3	CH
3	CH_3	H	H	OCH_3	OCH_3	CH
4	C_2H_5	H	H	CH_3	OCH_3	N
5	C_2H_5	H	H	OCH_3	OCH_3	CH
6	CH_2CF_3	H	H	OCH_3	OCH_3	CH
7	i-C_3H_7	H	H	OCH_3	OCH_3	CH
8	c-C_3H_7	H	H	OCH_3	OCH_3	CH
9	$-CH_2CH{=}CH_2$	H	H	OCH_3	OCH_3	CH
10	$-CH_2CH{=}CH_2$	H	H	OCH_3	OCH_3	N
11	$-CH_2C{\equiv}CH$	H	H	OCH_3	OCH_3	CH
12	C_4H_9	H	H	OCH_3	OCH_3	CH
13	$(CH_2)_2OCH_3$	H	H	OCH_3	OCH_3	CH
14	$(CH_2)_2OCH_3$	H	H	OCH_3	OCH_3	N
15	$CH_2CO_2CH_3$	H	H	OCH_3	OCH_3	CH
16	C_6H_5	H	H	OCH_3	OCH_3	CH
17	CH_3	CH_3	H	CH_3	OCH_3	CH
18	CH_3	CH_3	H	CH_3	OCH_3	N
19	CH_3	CH_3	H	OCH_3	OCH_3	CH
20	CH_3	CH_3	H	OCH_3	OCH_3	N
21	C_2H_5	CH_3	H	OCH_3	OCH_3	CH
22	C_2H_5	C_2H_5	H	OCH_3	OCH_3	CH
23	C_2H_5	C_2H_5	H	OCH_3	OCH_3	N
24	CH_2CF_3	CH_3	H	OCH_3	OCH_3	CH
25	OCH_3	CH_3	H	OCH_3	OCH_3	CH
26	OCH_3	CH_3	H	CH_3	OCH_3	N
27	CO_2CH_3	CH_3	H	OCH_3	OCH_3	CH
28	C_6H_5	CH_3	H	OCH_3	OCH_3	CH
29	4-Cl-C_6H_4	CH_3	H	OCH_3	OCH_3	CH
30	2,4-F_2-C_6H_3	CH_3	H	OCH_3	OCH_3	CH

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Table I *Continued*

Compd.	R^1	R^2	R^3	X^1	X^2	Z
31	$-CH_2CH_2CH_2CH_2-$		H	OCH_3	OCH_3	CH
32	$-CH_2CH_2OCH_2CH_2-$		H	OCH_3	OCH_3	CH
33	$-CH_2CH_2OCH_2CH_2-$		H	OCH_3	OCH_3	N
34	$-CH_2CH_2SCH_2-$		H	OCH_3	OCH_3	CH
35	$-CH_2CH_2CH_2CH_2-$		H	CH_3	OCH_3	N
36	CH_3	H	CH_3	OCH_3	OCH_3	CH
37	CH_3	H	$N(CH_3)_2$	OCH_3	OCH_3	CH
38	CH_3	H	$N(CH_3)_2$	CH_3	OCH_3	N
39	CH_3	CH_3	F	OCH_3	OCH_3	CH
40	CH_3	CH_3	Cl	OCH_3	OCH_3	CH
41	CH_3	CH_3	Br	OCH_3	OCH_3	CH
42	CH_3	CH_3	CH_3	OCH_3	OCH_3	CH
43	CH_3	CH_3	C_2H_5	OCH_3	OCH_3	CH
44	CH_3	CH_3	CH_2F	OCH_3	OCH_3	CH
45	CH_3	CH_3	CHF_2	OCH_3	OCH_3	CH
46	CH_3	CH_3	CF_3	OCH_3	OCH_3	CH
47	CH_3	CH_3	$N(CH_3)_2$	OCH_3	OCH_3	CH
48	CH_3	CH_3	$N(CH_3)C_2H_5$	OCH_3	OCH_3	CH
49	CH_3	CH_3	OCH_3	OCH_3	OCH_3	CH
50	CH_3	CH_3	OC_2H_5	OCH_3	OCH_3	CH
51	CH_3	CH_3	OCH_2CF_3	OCH_3	OCH_3	CH
52	CH_3	CH_3	SCH_3	OCH_3	OCH_3	CH
53	CH_3	CH_3	SO_2CH_3	OCH_3	OCH_3	CH
54	CH_3	CH_3	CHO	OCH_3	OCH_3	CH
55	CH_3	CH_3	CH_2OCH_3	OCH_3	OCH_3	CH
56	CH_3	CH_3	$CH_2OCH_2CF_3$	OCH_3	OCH_3	CH

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

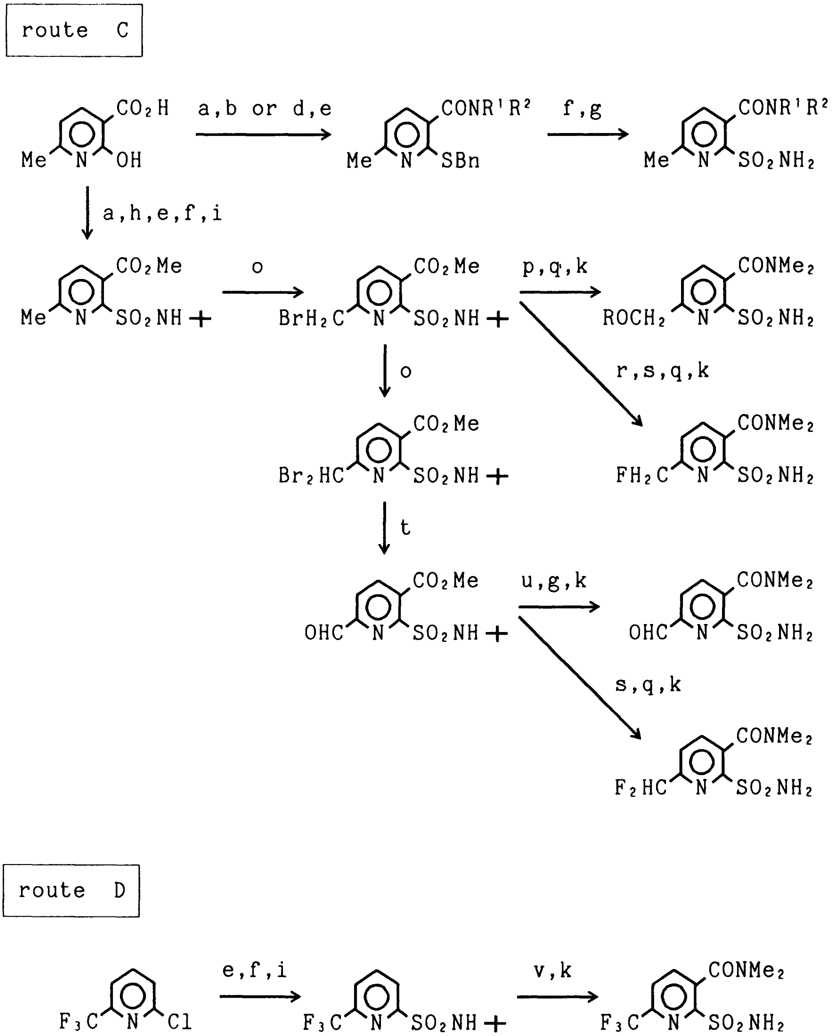

route A
CONHR¹
N Cl
a,b
c
CO₂H
N Cl
a,d
CONR¹R²
N Cl
e
CONR¹R²
N SBn
a,h,e,f,i
f,g
CO₂Me
N SO₂NH+
j or g
CONR¹R²
N SO₂NH+
k
CONR¹R²
N SO₂NH₂
route B
CF₃
Cl N Cl
l,a, b or d
CONR¹R²
Cl N Cl
m,e
CONR¹R²
BnO N SBn
n
CONR¹R²
HO N SBn
f,i
CONR¹R²
HO N SO₂NH+
a,R³H
CONR¹R²
R³ N SO₂NH+
k
CONR¹R²
R³ N SO₂NH₂

a) $SOCl_2$, b) R^1NH_2/CH_2Cl_2, c) $NaH, R^2X/THF$, d) $NH(R^1)R^2/CH_2Cl_2$ e) $BnSH, K_2CO_3/DMSO$, f) Cl_2/aq.AcOH, g) NH_3/CH_2Cl_2, h) MeOH, NEt_3/EDC, i) $t\text{-}BuNH_2/CH_2Cl_2$, j) $Me_2AlN(R^1)R^2$/benzene-CH_2Cl_2, k) CF_3CO_2H, l) 1.$AlCl_3$/EDC 2.H_2SO_4, m) $BnOH, K_2CO_3/DMSO$, n) c.HCl

Scheme I Synthetic Routes of Sulfonamides

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006



o) NBS/CCl_4, p) RONa/ROH, q)$NH(R^1)R^2$/MeOH, r) $AgNO_3$/acetone-H_2O,

s) Et_2NSF_3/CH_2Cl_2, t) $AgNO_3$/EtOH-H_2O u) $HO(CH_2)_2OH$,TsOH,

v) n-BuLi, $ClCONMe_2$/THF

Scheme I *Continued*

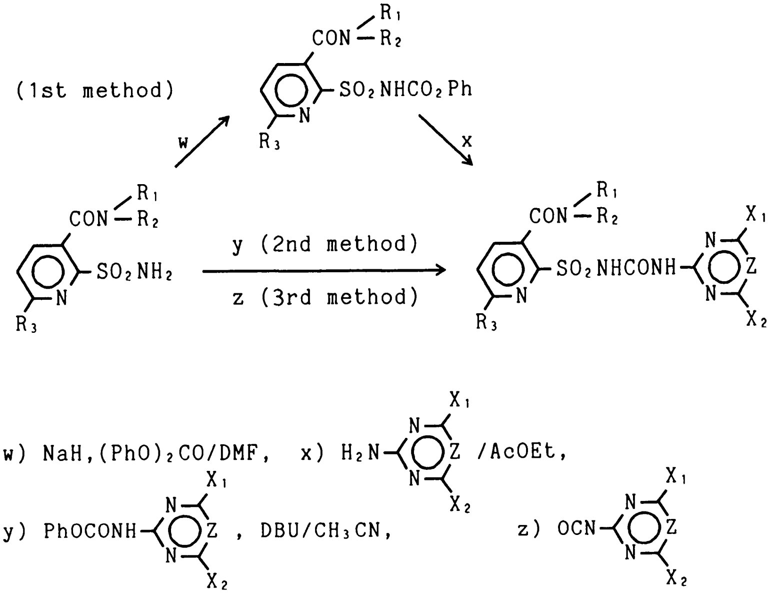
American Chemical Society
Library
1155 16th St., N.W.
Washington, D.C. 20036

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

prepared from 2,6-dichloro-3-trifluoromethylpyridine by the side-chain transhalogenation, were treated with benzyl alcohol to introduce benzyloxy protecting group at the 6-position by a nucleophilic substitution. The 6-benzyloxy compounds freed from approximately 10% of the corresponding 2-benzyloxy isomer, were reacted with benzylmercaptan to introduce the thioethereal linkage at 2-position, which was to be converted to a sulfonamide group.

The 6-hydroxyl compounds, obtained by deprotection of the benzyl group, were reacted with various nucleophiles to introduce a substituent R^3 at the 6-position. By route B, the precursors for compounds **37**∼**41**, and **47**∼**53** were prepared. Precursors for compounds **36**, **42** and **43** bearing alkyl groups and compounds **55** and **56** bearing alkoxymethyl groups as R^3 at 6-position were prepared by the first two methods in route C, respectively. Synthetic methods for precursors for the 6-fluoromethyl (compound **44**), 6-formyl (compound **54**) and 6-difluoromethyl (compound **45**) derivatives are also shown in route C. A precursor for compound **46** bearing a trifluoromethyl group at 6-position was prepared according to route D.

The sulfonamide precursors were converted to sulfonylurea compounds by one of three coupling processes shown in Scheme II. The first method is the condensation of the aminopyrimidines or aminotriazines with the phenyl N-pyridylsulfonylcarbamates derived from sulfonamide precursors. The second and the third methods are the condensation of the sulfonamides with either the phenyl carbamates or the isocyanates which were derived from either aminopyrimidines or aminotriazines.



Scheme II Coupling Process

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Quantitative Structure Activity Relationships

Analyses of quantitative structure activity relationship were carried out by the adaptive least-squares method (*4*). Herbicidal activities of afore mentioned SL-950 analogs were divided into three classes according to the intensity against soybean, cocklebur, morning-glory, smartweed and pigweed by foliar application at the ratio of 125 g a.i./ha. In Table II, rank 3 means the most effective class while rank 1 indicates no herbicidal effect.

Equation (1) is the best equation (correlation coefficient is 0.89 and is satisfactory) obtained for compounds **1~34** which have no substituents at the 6-position on the pyridine ring.

$$\begin{aligned} L = {} & \underset{(0.628)}{1.056\,\Delta\log P} - \underset{(2.383)}{0.279\,(\Delta\log P)^2} - \underset{(1.033)}{0.007\,Vw\,(R^1)} \\ & - \underset{(0.207)}{0.036\,Vw\,(R^2)} - \underset{(0.248)}{1.380\,I} + 1.680 \cdots\cdots \quad (1) \end{aligned}$$

$N = 34$ (3-grades), $Rs = 0.89$, $\varepsilon = 0.160$, $Mis = 3(0)$
Rs(leave-one-out) $= 0.74$, $\Delta\log P_{opt} = 1.892$

In the equation (1), L represents the discriminant function and the value in parenthesis under each term indicates the contribution factor which is the value of coefficient multiplied by the standard deviation. Physico-chemical parameters for each compound are shown in Table II. $Vw(R^1)$ is the van der Waals volume of substituent R^1 calculated by Bondi's method (*5*). R^1 is dedicated to the more bulky group in comparison with R^2 group. $Vw(R^2)$ is the van der Waals volume of R^2 group in excess of that of a methyl group. In other words, in the case of a hydrogen or a methyl group as R^2, $Vw(R^2)$ was estimated as 0. $\Delta\log P$ is the summation of the 1-octanol/water partition coefficients calculated by Cippen's method (*6*) for pyridine ring and the other heterocyclic moiety except the sulfonylurea bridge. N is the number of compounds. Rs is the Spearman rank correlation coefficient. ε is the dispersion of error. Mis is the number misclassified. The figure in parenthesis after the value of Mis is the number misclassified by two grades. I is a dummy parameter for heterocyclic moiety, that is, I is 0 for pyrimidine and 1 for triazine.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Table II Physico-chemical Parameters Used for Equations (1) and (2)

Compds.	rank of activity		$Vw(R^1)$	$Vw(R^2)$	$Vw(R^3)$	$\Delta\log P$	I
	obsd.	pred.					
1	2	2	3.45	0	3.45	0.784	0
2	2	3	13.68	0	3.45	1.125	0
3	3	3	13.68	0	3.45	1.125	0
4	1	1	23.91	0	3.45	2.298	1
5	2	3	23.91	0	3.45	1.610	0
6	2	2	32.16	0	3.45	1.930	0
7	2	2	34.14	0	3.45	1.899	0
8	2	2	27.24	0	3.45	1.503	0
9	2	2	30.62	0	3.45	1.758	0
10	1	1	30.62	0	3.45	1.960	1
11	3	2	23.72	0	3.45	1.290	0
12	2	2	44.37	0	3.45	2.533	0
13	2	2	37.84	0	3.45	0.758	0
14	1	1	37.84	0	3.45	0.960	1
15	1	1	42.29	0	3.45	-0.091	0
16	2	2	47.37	0	3.45	2.626	0
17	2	3	13.68	0	3.45	1.596	0
18	1	1	13.68	0	3.45	2.154	1
19	3	3	13.68	0	3.45	1.466	0
20	1	1	13.68	0	3.45	1.668	1
21	3	3	23.91	0	3.45	1.951	0
22	2	2	23.91	10.25	3.45	2.436	0
23	1	1	23.91	10.25	3.45	2.638	1
24	2	2	32.16	0	3.45	2.271	0
25	3	3	17.38	0	3.45	1.466	0
26	1	1	17.38	0	3.45	2.154	1
27	2	2	32.06	0	3.45	1.408	0
28	2	2	47.37	0	3.45	2.967	0
29	2	2	56.16	0	3.45	3.562	0
30	2	2	52.87	0	3.45	3.308	0

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Table II ***Continued***

Compds.	rank of activity		$Vw(R^1)$	$Vw(R^2)$	$Vw(R^3)$	Δ log P	I
	obsd.	pred.					
31	2	2	20.46	6.80	3.45	2.040	0
32	2	2	24.16	6.80	3.45	0.751	0
33	1	1	24.16	6.80	3.45	0.953	1
34	2	2	31.26	0	3.45	2.404	0
35	1	1	20.46	6.80	3.45	2.242	1
36	3	3	13.68	0	13.67	1.399	0
37	3	3	13.68	0	31.67	1.563	0
38	1	1	13.68	0	31.67	2.251	1
39	3	3	13.68	0	5.72	1.775	0
40	3	3	13.68	0	11.62	1.997	0
41	3	3	13.68	0	14.40	2.298	0
42	3	3	13.68	0	13.67	1.740	0
43	3	3	13.68	0	23.90	2.390	0
44	3	3	13.68	0	15.95	1.648	0
45	3	3	13.68	0	18.98	2.131	0
46	3	3	13.68	0	21.93	2.626	0
47	3	3	13.68	0	31.67	1.904	0
48	2	2	13.68	0	41.89	2.389	0
49	3	3	13.68	0	16.87	1.611	0
50	3	3	13.68	0	27.10	2.096	0
51	2	2	13.68	0	38.84	2.416	0
52	3	3	13.68	0	24.47	2.304	0
53	1	2	13.68	0	37.92	0.434	0
54	2	3	13.68	0	15.15	1.649	0
55	3	2	13.68	0	27.10	1.194	0
56	2	2	13.68	0	49.06	1.999	0

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Since the coefficients for Vw(R^1) and Vw(R^2) are negative, the larger R^1 and R^2 decrease the herbicidal activity. The optimum value for Δlog P will exist because the equation is quadratic for it. Calculated optimum value for Δlog P is 1.892. This value is larger than the Δlog P for SL-950 (1.466). However, from the fact that large R^1 and R^2 decrease the activity, the result of the combined effect of Δlog P and Vw suggests that SL-950 shows the highest activity.

Next, we carried out a QSAR analysis for SL-950 analogs including sulfonylureas which have a substituent as R^3 to analyze the contribution by that group. The best equation (2) for compounds **1**$\sim$**56** is obtained by the procedure shown below.

$$L = \underset{(0.428)}{0.953\ \Delta\log P} - \underset{(1.449)}{0.233\ (\Delta\log P)^2} - \underset{(1.751)}{0.013\ Vw\ (R^1)}$$

$$- \underset{(0.179)}{0.028\ Vw\ (R^2)} - \underset{(0.716)}{0.005\ Vw\ (R^3)} - \underset{(0.211)}{1.436\ I} + 1.938 \cdots\cdots (2)$$

$$N = 56,\quad Rs = 0.89,\quad \varepsilon = 0.191,\quad Mis = 7(0)$$
$$Rs(\text{leave-one-out}) = 0.81,\quad \Delta\log P_{opt} = 2.006$$

To obtain equation (2), the same parameters as that of the equation (1) were used except Vw(R^3) which is van der Waals volume of R^3 group. It was confirmed that there were no correlations between Δlog P and each Vw. All of the terms for Vw are again negative and the equation is also quadratic for Δ log P as was experienced for the equation (1). The values of contribution factor indicate that the contribution of Vw(R^1) and Vw(R^3) is important. Especially, Vw(R^1) has the largest contribution factor among all of the parameters in the equation. The order of flexibility for the site of receptor is R^3, R^1, R^2 according to the absolute values of coefficient for Vw. The optimum value for Δlog P was calculated to be 2.006.

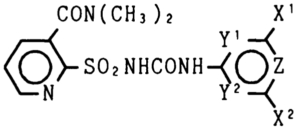
In the equations (1) and (2) we used a dummy parameter concerning heterocycle moiety except log P, in which the contribution of heterocycle moiety is partly involved. With the intention of a thorough investigation of the contribution of the heterocyclic moiety to the herbicidal activity, we carried out another QSAR analysis using 15 compounds in Table III bearing a dimethylcarbamoyl group at the 3-position of pyridine ring keeping the left-half of the structure fixed. In Table III, X^1 represents the smaller group in comparison with X^2 group. According to the result of leave-one-out prediction, equation (3) was selected. $\Sigma\sigma$ in the equation is the summation of Hammett's electronic parameters (*7*) of each position of the heterocycle ring. V is the addition of van der Waals volume of both X^1 in excess of that of OCH_3 and Z in excess of CH. From the equation a certain electronic interaction between the heterocycle ring and receptor was elucidated in addition to the steric effect for X^1 and Z.

$$L = \underset{(1.37)}{7.18\ \Sigma\sigma} - \underset{(5.95)}{1.61\ (\Sigma\sigma)^2} - \underset{(1.02)}{0.168\ V} - 6.15 \quad \cdots\cdots \quad (3)$$

$$N = 15,\quad Rs = 0.92,\quad \varepsilon = 0.217,\quad Mis = 1(0)$$
$$Rs(\text{leave-one-out}) = 0.72,\quad \Sigma\sigma_{opt} = 2.23$$

Contribution factors of each term show that the contribution of electronic parameter is larger than that of steric effect. The optimum value for $\Sigma\sigma$ was calculated to be 2.23 from the equation.

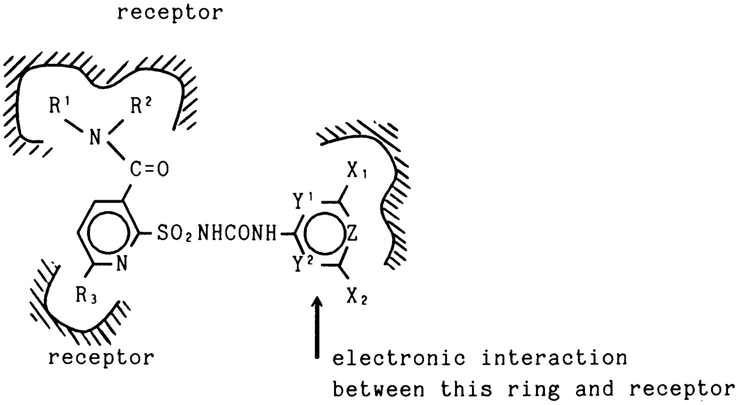
Table III Compounds and Physico-chemical Parameters for Equation (3)



Compd.	Y^1	Y^2	Z	X^1	X^2	rank of activity obsd.	rank of activity pred.	$\Sigma\sigma$	V
17	N	N	CH	CH_3	OCH_3	2	2	1.91	0
18	N	N	N	OCH_3	OCH_3	1	1	3.03	0
19	N	N	CH	OCH_3	OCH_3	3	2	2.10	0
26	N	N	N	CH_3	OCH_3	1	1	2.84	0
57	N	N	CH	OCH_3	OC_2H_5	2	2	2.08	0
58	N	N	CH	OCH_3	$OCHF_2$	2	2	2.29	0
59	N	N	CH	OCH_3	SCH_3	2	2	2.13	0
60	N	N	CH	Cl	OCH_3	2	2	2.35	0
61	N	N	CH	$OCHF_2$	$OCHF_2$	1	1	2.48	5.51
62	N	N	CH	SCH_3	SCH_3	1	2	2.16	7.60
63	N	N	CH	CH_3	CH_3	1	1	1.72	0
64	N	N	CF	OCH_3	OCH_3	1	2	2.16	2.27
65	N	CH	CH	CF_3	CF_3	1	1	1.79	5.06
66	CH	CH	N	OCH_3	CF_3	1	1	1.48	0
67	CH	CH	N	H	CF_3	1	1	1.36	0

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

The results of the afore-mentioned correlation analyses can be summarized in the receptor mapping shown in Scheme III. Equation (1) indicates that the pyridine ring binds with receptor bearing some hydrophobic character. Especially the binding site of the receptor which surrourds the 3-position substituent of pyridine ring could accomodate only a limited numbers of atoms, elucidating that methyl group is the most desirable as the substituent R^1 and R^2. Since the steric contribution of substituent R^3 as well as that of R^1 was found to be important by equation (2), the binding region around R^3 can be size-limited. From the equation (3) were suggested two points. Since an optimum value exists for the electronic parameter σ, there must be an electronic interaction between the heterocycle moiety and receptor dipole, and that this interaction is sterically affected at the place near substituent X^1 and nuclear atom Z.



Scheme III Interpretation of the QSAR Analyses

Conclusion

The result of QSAR analyses was summarized as the receptor mapping in Scheme III. The optimum values for Δlog P was obtained and the steric effect for R^1, R^2, R^3 X^1 and Z was observed. An electronic interaction between the heterocycle moiety and the receptor was also suggested from the equation (3). The three equations were consistent with the fact that SL-950 was the most desirable herbicidal compound.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Literature Cited

1. Murai, S.; Haga, T.; Fujikawa, K.; Sakashita, N.; Kimura, F., Ed.; ACS Symposium Series No. 443; American Chemical Society: Washington, D.C., 1991; p98.
2. Murai, S.; Haga, T.; Sakashita, N.; Honda, C.; Nakamura, Y.; Honzawa, S.; Tsujii, Y.; Kimura, F.; Fujikawa, K.; Nishiyama, R. *J. Pestic. Sci.*, Submitted.
3. Kimura, F.; Haga, T.; Sakashita, N.; Honda, C.; Murai, S. European Patent 0 232 067, 1987.
4. Moriguchi, I.; Komatsu, K. *Eur. J. Med. Chem.*, **1981**, 19.
5. Bondi, A. *J. Phys. Chem.*, **68, 1964**, 68, 441.
6. Ghose, A. K.; Crippen, G. M. *J. Comput. Chem.*, **1986**, 7, 565.
7. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.*, **1991**, 91, 165.

RECEIVED April 27, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch006

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Chapter 7

Novel *N*-Substituted Imidazolinones

Synthesis and Herbicidal Activity

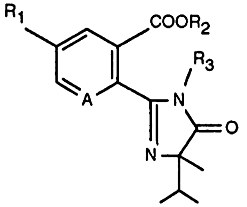
M. A. Guaciaro, M. Los, D. L. Little, P. A. Marc, and L. Quakenbush

**Agricultural Research Division, American Cyanamid Company,
P.O. Box 400, Princeton, NJ 08543–0400**

In an effort to prepare new imidazolinone herbicides with the required combination of weed control, crop safety and reduced soil persistence, various novel N-hydroxy, N-chloro- and N-cyano-imidazolinones were synthesized. The N-hydroxyimidazolinones, although interesting from a synthetic standpoint, did not show a significant advantage over their imidazolinone counterparts in the greenhouse. The N-chloroimidazolinones showed better weed control and crop safety than their imidazolinone precursors in several instances but showed no evidence of reduced soil persistence. The N-cyanoimidazolinones exhibited excellent weed control and crop selectivity with evidence of reduced soil persistence, depending upon the nature of the carboxylate substituent.

Previous papers in the imidazolinone area have discussed the effects on herbicidal activity produced by changes in the aryl rings, the aryl ring substituents, the nature of the imidazolinone carbonyl and the alkyl substituents on the imidazolinone ring (*1-22*).

In the area covered by this paper, it was reasoned that substitution of various functional groups, such as chloro, hydroxyl and cyano on the imidazolinone nitrogen might afford new herbicides with different weed control/crop safety spectra. In addition, it was reasoned that certain electron-withdrawing N-substituents, in particular cyano, might make the imidazolinone ring more susceptible to breakdown in the soil, thus reducing the soil persistence of the herbicide.



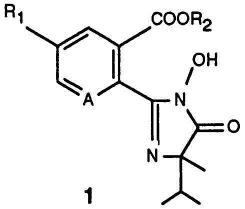
A = CH, N
R_1 = H, alkyl
R_2 = H, alkyl, benzyl, furfuryl, allyl
R_3 = Cl, OH, CN

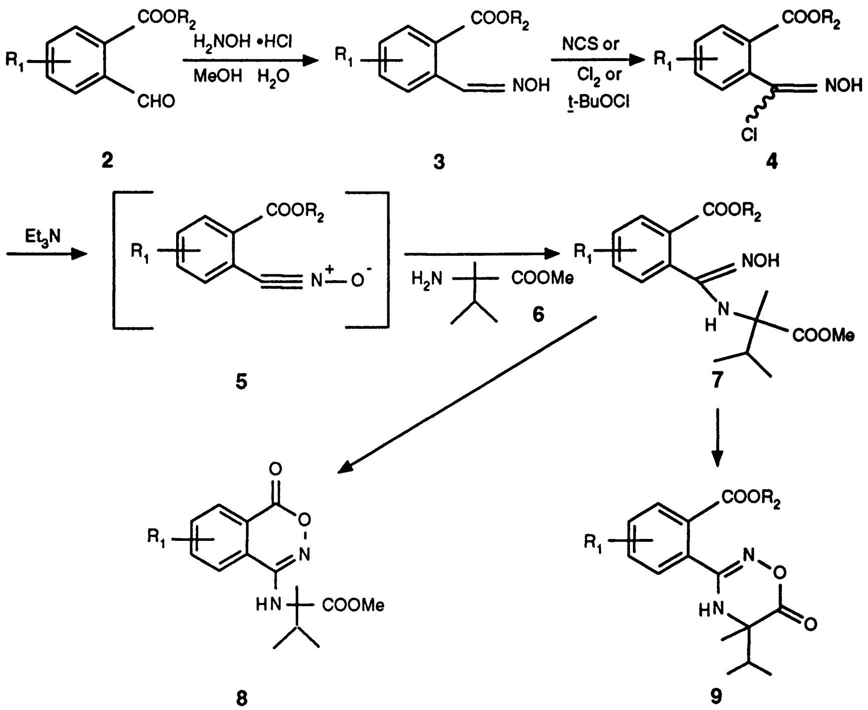
0097–6156/92/0504–0056$06.00/0

This paper will discuss the synthesis and herbicidal activity of various N-hydroxy-, N-chloro- and N-cyanoimidazolinones (*23*).

N-Hydroxyimidazolinones

Synthesis. Since there was no existing method for the preparation of N-hydroxyimidazolinones of this type, we proposed the following synthesis. Oximes of type **3** can be prepared from the readily available aldehydes **2** (*24*). Chlorination of these oximes, using NCS (*24*, *25*), chlorine (*26*) or *t*-butylhypochlorite (*27*) would afford chloro-oximes of type **4**. We reasoned that the chloro-oximes **4**, when treated with triethylamine in the presence of aminoester **6**, would form intermediates of type **7** which could cyclize to either bezoxazinones **8** or oxadiazinones **9**.

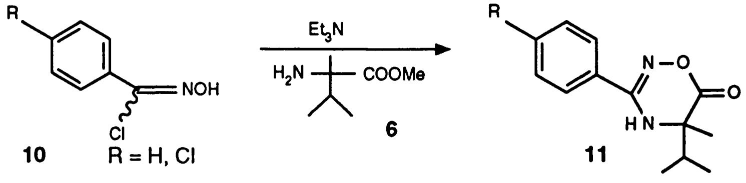

R1
COOR2
OH
N
A
O
N
1


COOR2
CHO
R1
2
H2NOH •HCl
MeOH H2O
NOH
3
NCS or
Cl2 or
t-BuOCl
Cl
4
Et3N
N+—O-
5
H2N
COOMe
6
NOH
H
N
7
O
N
HN
8
N
O
HN
9

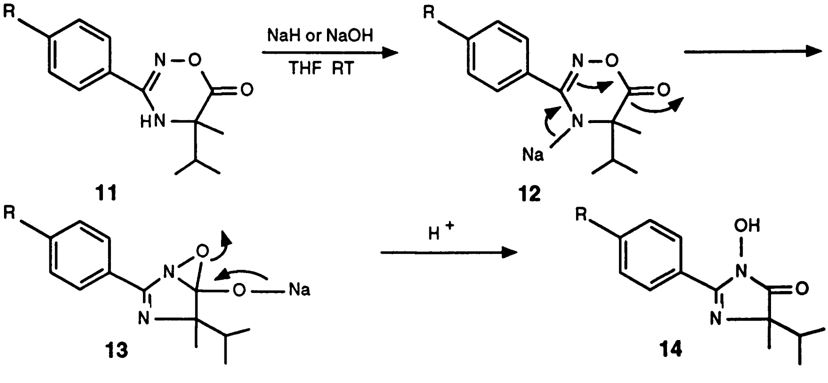
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Oxadiazinones of type **11**, with no *ortho*-carboxyl group, had been prepared previously in our labs (Los, M., American Cyanamid Co., Agricultural Research Division, unpublished data, 1976) using the nitrile oxide cycloaddition shown below (*28*). These oxadiazinones show characteristic carbonyl bands in their IR spectra at 1750 cm-1 and fragment in the mass spectrometer with loss of carbon dioxide.



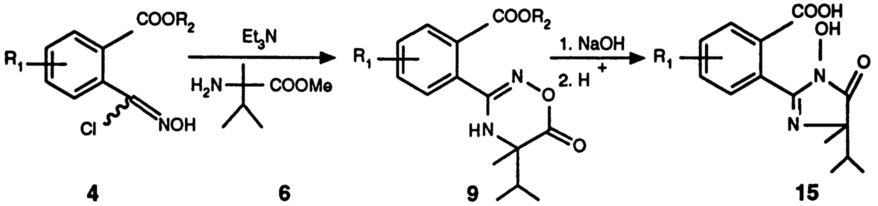
We subsequently discovered that treatment of oxadiazinones of type **11** with sodium hydride in THF afforded N-hydroxyimidazolinones of type **14**, presumably via the ring contraction mechanism shown below. This ring contraction may also be accomplished with sodium hydroxide. These N-hydroxyimidazolinones exhibit proton and carbon NMR spectra which are quite similar to NMR spectra of the imidazolinones with respect to the chemical shifts and coupling constants of the methyl and isopropyl protons and with respect to the chemical shifts of the imidazolinone ring carbonyl and ring carbons.

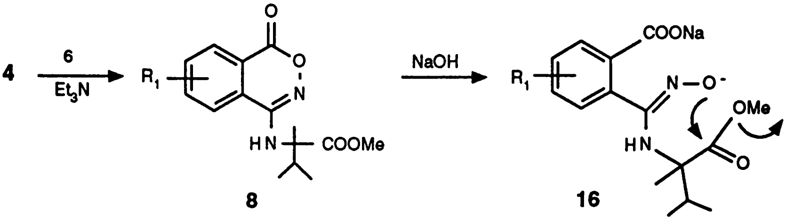


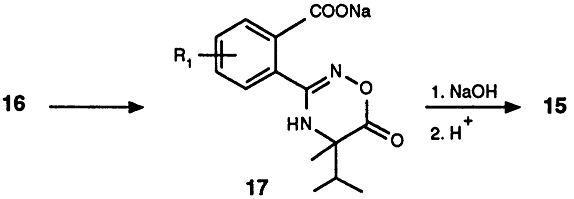
Therefore, if the cycloaddition of the nitrile oxide derived from chloro-oxime **4** with aminoester **6** afforded oxadiazinones of type **9**, we reasoned that base treatment of these oxadiazinones would afford the target compounds of type **15**. If, on the other hand, benzoxazinones of type **8** formed, then base treatment of them might also afford targets of type **15** via intermediates **16** and **17**.

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

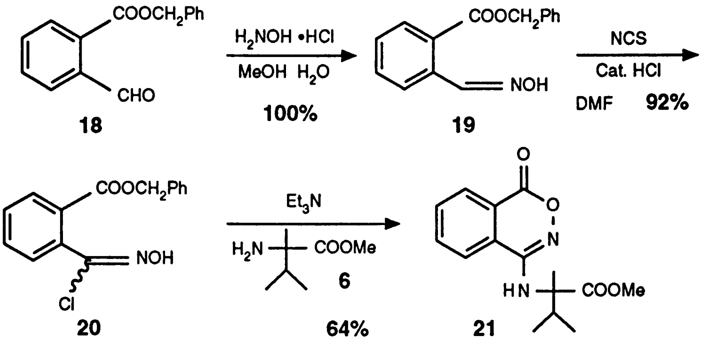
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007


COOR₂
R₁
Cl
NOH
Et₃N
H₂N
COOMe
1. NaOH
2. H⁺
HN
N
O
COOH
OH
4
6
9
15


4
6
Et₃N
R₁
O
N
HN
COOMe
8
NaOH
COONa
N—O⁻
OMe
16

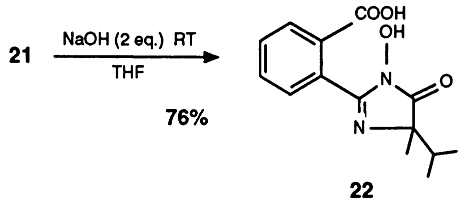

16
COONa
R₁
N
O
HN
17
1. NaOH
2. H⁺
15

Toward this end, treatment of aldehyde **18** with hydroxylamine hydrochloride afforded oxime **19**, which was chlorinated with NCS to afford **20** in high yield. Treatment of **20** with triethylamine in the presence of aminoester **6** afforded benzoxazinone **21**, which was identified on the basis of its IR (NH: 3290 cm-1, carbonyls: 1725 and 1705 cm-1), proton NMR (loss of benzyl ester; retention of methyl ester singlet) and mass spectrum (loss of carbon dioxide).

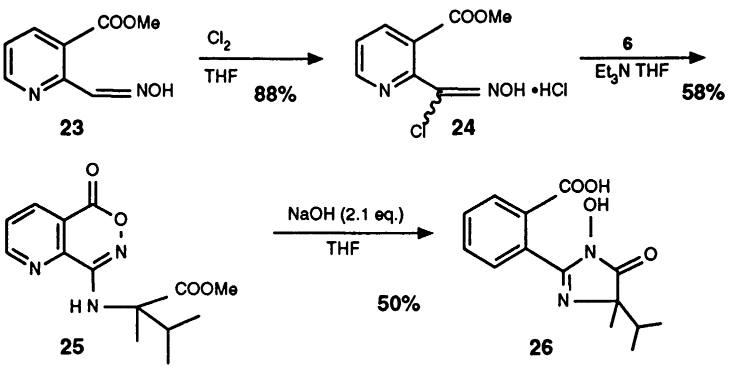

COOCH₂Ph
CHO
18
H₂NOH •HCl
MeOH H₂O
100%
NOH
19
NCS
Cat. HCl
DMF 92%
Cl
20
Et₃N
H₂N
COOMe
6
64%
O
N
HN
COOMe
21

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Treatment of **21** with excess sodium hydroxide at room temperature afforded one product. The product was identified as hydroxyimidazolinone **22** on the basis of its NMR, IR and mass spectral data. The structural assignment was confirmed by a single crystal X-ray analysis (Whittle, R. R., Oneida Research Services, New Hartford, NY, 1985, unpublished data).



In the imazapyr area, chlorination of oxime **23** afforded **24** in high yield. Treatment of chloro-oxime **24** with triethylamine and aminoester **6** afforded **25** in 58% yield. Hydroxyimidazolinone **26** was isolated from the reaction of **25** with sodium hydroxide in 50% yield after recrystallization.

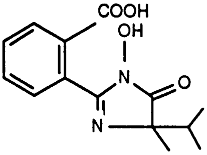


Biological Activity. Table I compares hydroxyimidazolinone **22** to its imidazolinone counterpart **27** preemergence at 500 g/ha. Compound **22** showed good overall grass control but was less effective than **27** in controlling morningglory and velvetleaf in the broadleaf area. Both compounds were toxic to crops.

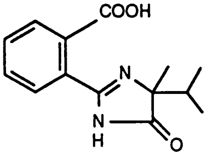
Table II compares hydroxyimidazolinone **26** to imazapyr **28** postemergence at 63 g/ha. Compound **26** was safer than imazapyr on crops with safety on sunflower and marginal safety on corn and soybeans. It was less effective than **28** in controlling broadleaves. Preemergence, **26** behaved as a total vegetation control agent down to 63 g/ha but was less effective than imazapyr in controlling broadleaves.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Table I. Comparison of hydroxyimidazolinone 22 to imidazolinone 27 at 500 g/ha preemergence



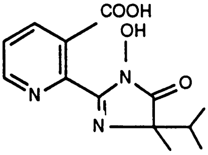
22



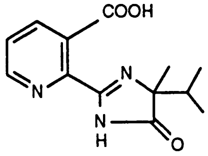
27

Compound	% Control Grasses	 Broadleaves	% Injury Crops
22	71	53	65
27	71	66	86

Table II. Comparison of hydroxyimidazolinone 26 to imazapyr 28 at 63 g/ha postemergence



26



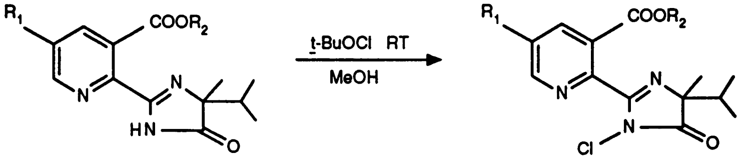
28 imazapyr

Species	% Injury or % Control 26	 28
Sunflower	0	100
Soybean	22	93
Corn	22	100
Matricaria	0	81
Velvetleaf	67	96
Ragweed	0	71
Morningglory	55	96
Field Bindweed	0	100
Foxtail	100	100
Quackgrass	33	98
Wild Oats	78	100
Purple Nutsedge	0	86
Barnyardgrass	100	94

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

N-Chloroimidazolinones

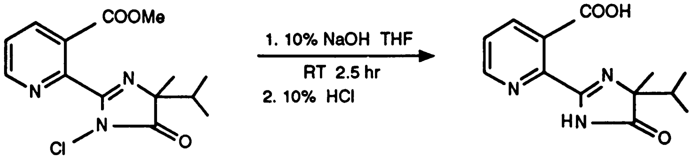
Synthesis. N-Chloroimidazolinones of type **29** were prepared by treating the appropriate imidazolinyl carboxylate with *tert*-butyl hypochlorite at room temperature with the exclusion of light.



R_1 = H, alkyl
R_2 = alkyl

29

When chloroimidazolinone **30** was treated with dilute sodium hydroxide in an attempt to hydrolyze the methyl ester, cleavage of the nitrogen-chlorine bond also occurred, affording imazapyr **28** as the sole product. These results imply that the chloroimidazolinones might degrade in the plant or soil to their parent imidazolinones with no reduction in soil persistence.



30 Stable at pH 6-7

28

Herbicidal Activity. Chloroimidazolinone **30** behaved as a total vegetation control agent preemergence but was less effective than its parent imidazolinone.

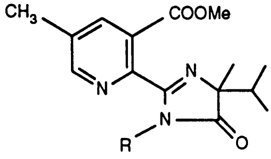
Table III compares chloroimidazolinone **32** to imidazolinone **33** preemergence at 16 g/ha. Introduction of a chlorine onto the imidazolinone ring in this case affords a compound with better overall preemergence weed control. Compound **32** showed better control of velvetleaf, wild mustard, field bindweed, quackgrass, wild oats and purple nutsedge with improved safety on soybeans.

N-Cyanoimidazolinones

The rationale for placement of a cyano group on the imidazolinone nitrogen was not only to study the effect of this substitution on herbicidal activity, but also to determine whether the presence of an N-cyano group would make the imidazolinone ring more susceptible to ring opening and hence to detoxification.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Table III. Comparison of chloroimidazolinone 32 to imidazolinone 33 preemergence at 16 g/ha



32 R = Cl

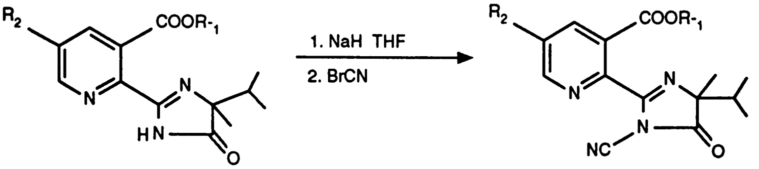
33 R = H

Species	% Injury or % Control 32	33
Soybeans	6	19
Wheat	22	3
Velvetleaf	89	73
Ragweed	0	4
Wild Mustard	100	89
Morningglory	55	44
Field Bindweed	100	70
Quackgrass	100	26
Wild Oats	89	67
Purple Nutsedge	89	72
Foxtail	78	72
Barnyardgrass	11	16

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Figure 1 shows two potential degradation pathways for N-cyanoimidazolinones of type **34**. Hydrolysis would produce acids of type **35**, which could undergo nucleophilic attack at the imidazolinone C-2 position, affording intermediates of type **36**. In Pathway A, cyclization of **36** to tricycles of type **37** followed by formation of imides of type **38** could be followed by imide ring opening and loss of cyanide to afford open chain compounds of type **40**. Pathway B would afford **40** via ring opening of **36**, tautomerization of **39** and loss of cyanide. Open chain compounds of type **40** are known to have minimal to no herbicidal activity. Such a process would therefore result in reduced soil persistence.

Synthesis: Esters. Esters in this area can be prepared by treating the appropriate imidazolinone with sodium hydride followed by cyanogen bromide to afford the products shown below in yields ranging from 60 to 100%.



41 R_1 = Me R_2 = Me
42 R_1 = Et R_2 = p-methoxybenzyl
43 R_1 = Et R_2 = furfuryl
44 R_1 = Me R_2 = p-methoxybenzyl
45 R_1 = Me R_2 = allyl

Herbicidal Activity: Esters. Table IV compares cyanoimidazolinone **41** to its parent **33** postemergence at 63 g/ha. Both compounds were marginally safe on corn while **33** was slightly safer on wheat. Compound **41** was more effective in controlling morningglory and quackgrass while **33** was more effective in controlling field bindweed and much more effective in controlling purple nutsedge. Both compounds showed good control of velvetleaf, wild mustard, wild oats and foxtail.

Table V compares cyanoimidazolinone **42** to imidazolinone **46** preemergence at 125 g/ha. Although **46** showed good to excellent control of broadleaves and grasses, it was also injurious to the crops. Cyanoimidazolinone **42**, on the other hand, was totally safe on wheat and soybeans with 11% injury to corn and marginal safety on cotton. Compound **42** showed good control of velvetleaf, wild mustard, field bindweed, quackgrass, purple nutsedge, foxtail and barnyardgrass.

Table VI compares the furfuryl esters **43** and **47** preemergence at 63 g/ha. Imidazolinone **47** was more effective in controlling ragweed, morningglory and wild oats but **43** was safer on wheat and soybeans with good overall grass control. At 125 g/ha postemergence (Table VII) imidazolinone **47** showed better control of wild oats, velvet leaf and ragweed but was more toxic to soybeans than **43**. Cyanoimidazolinone **43** was completely safe on soybeans and controlled purple nutsedge more effectively than **47**.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

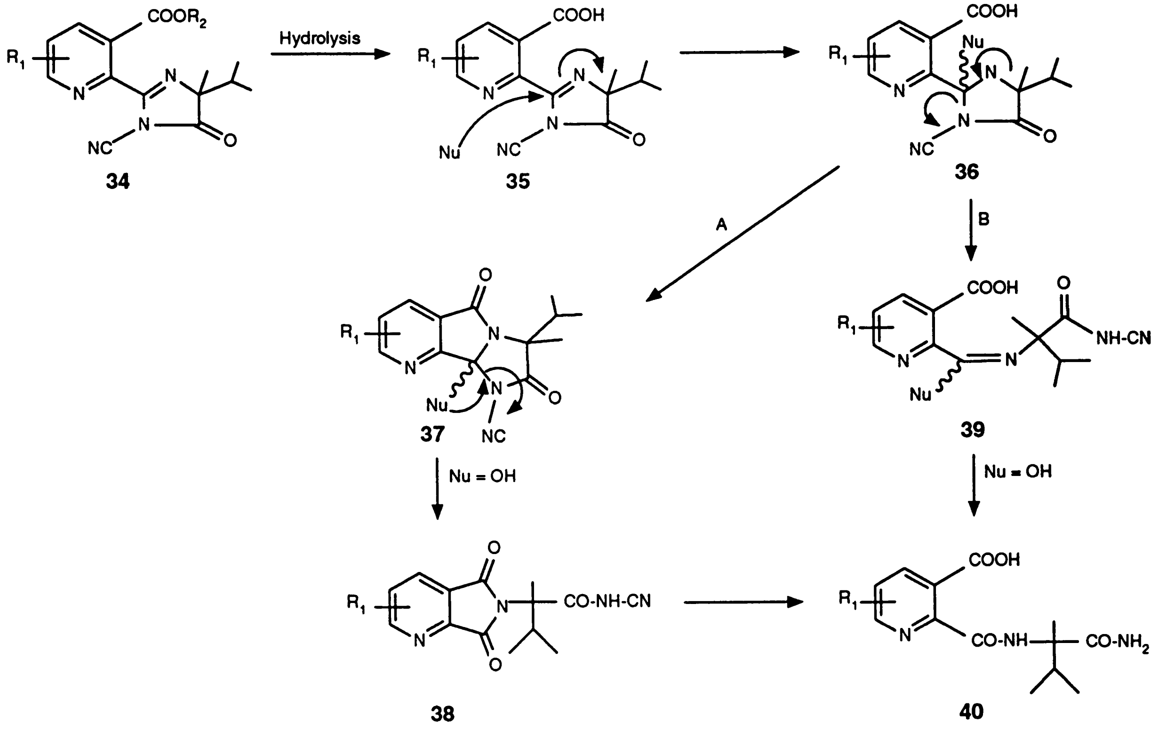
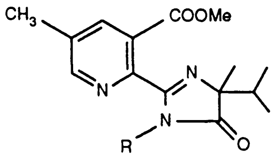

COOR$_2$
R$_1$
N
NC
O
34
Hydrolysis
COOH
Nu
35
36
A
B
37
Nu = OH
38
CO-NH-CN
39
NH-CN
40
CO-NH
CO-NH$_2$

Figure 1. Potential mechanisms of breakdown of N-cyanoimidazolinones in the plant and/or soil to non-toxic species.

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Table IV. Comparison of imidazolinone 33 to cyanoimidazolinone 41 postemergence at 63 g/ha



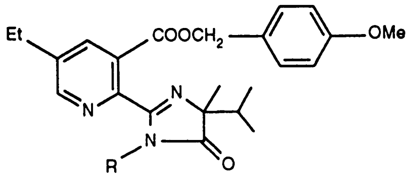
33 R = H

41 R = CN

Species	% Injury or % Control 33	41
Corn	22	22
Wheat	7.0	11
Ragweed	25	22
Velvetleaf	80	78
Wild Mustard	80	89
Morningglory	44	67
Field Bindweed	83	67
Quackgrass	17	44
Wild Oats	98	89
Foxtail	92	89
Purple Nutsedge	58	0
Barnyardgrass	55	67

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Table V. Comparison of imidazolinone 46 to cyanoimidazolinone 42 at 125 g/ha preemergence

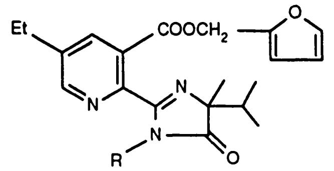


46 R = H

42 R = CN

Species	% Injury or % Control 46	 42
Wheat	67	0
Soybeans	17	0
Cotton	78	22
Corn	78	11
Velvetleaf	89	89
Ragweed	89	0
Wild Mustard	100	100
Morningglory	78	55
Field Bindweed	100	89
Quackgrass	100	100
Wild Oats	100	44
Purple Nutsedge	100	78
Foxtail	100	78
Barnyardgrass	100	78

Table VI. Comparison of cyanoimidazolinone 43 to imidazolinone 47 at 63 g/ha preemergence

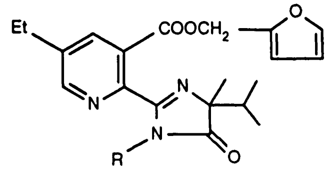


43 R = CN

47 R = H

	% Injury or % Control	
Species	43	47
Soybeans	0	17
Wheat	11	33
Velvetleaf	78	89
Ragweed	0	44
Morningglory	22	67
Field Bindweed	100	100
Quackgrass	67	100
Wild Oats	22	67
Purple Nutsedge	89	100
Foxtail	78	89
Barnyardgrass	67	78

Table VII. Comparison of cyanoimidazolinone 43 to imidazolinone 47 at 125 g/ha postemergence



43 R = CN

47 R = H

	% Injury or % Control	
Species	43	47
Soybeans	0	44
Velvetleaf	67	100
Ragweed	44	89
Wild Mustard	100	100
Morningglory	78	89
Field Bindweed	100	89
Quackgrass	78	67
Wild Oats	33	78
Purple Nutsedge	89	44
Foxtail	100	100
Barnyardgrass	100	100

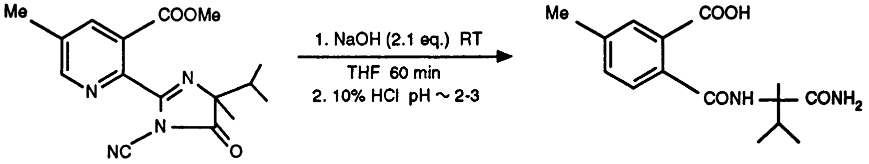
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Table VIII compares the *para*-methoxybenzyl esters **44** and **48** at 63 g/ha postemergence. Cyanoimidazolinone **44** was more effective in overall broadleaf control and significantly safer on soybeans and corn.

A comparison of allyl ester **45** to its parent **49** at 32 g/ha preemergence (Table IX) shows that cyanoimidazolinone **45** was less effective than **49** in controlling quackgrass and barnyardgrass but was superior to **49** in terms of corn safety.

We discovered that esters of the cyanoimidazolinones are unstable under conditions which do not normally affect the imidazolinones. When **41** was treated with dilute sodium hydroxide at room temperature in hopes of hydrolyzing the methyl ester, hydrolysis and ring opening occurred, affording acid diamide **50**.



41 **50**

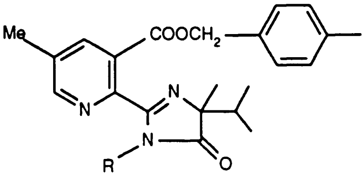
When **41** was applied in the field postemergence to wild oats and wheat at 50 g/ha it showed excellent control of wild oats and complete safety on wheat, outperforming its imidazolinone counterpart. Sixteen to nineteen weeks after treatment, the plots were planted with rape and sugarbeets. Four weeks later the plots showed much injury to the sugarbeets and rape. These results indicate that methyl ester **41** was undergoing little if any breakdown in the soil after 20-23 weeks. The instability of this cyanoimidazolinone at elevated pH is not an indication of reduced soil persistence.

We have evidence that suggests that the rate of breakdown or half-life of the imidazolinone esters is related to the nature of the ester and also to the substituents on the aryl ring (unpublished data, American Cyanamid Co., Agricultural Research Division). We are currently studying the rates of breakdown of other esters in the cyanoimidazolinone area with various substituents on the pyridine ring to determine if any compounds show the required combination of excellent weed control, crop selectivity and reduced soil persistence.

Synthesis: Acid Salts. It was thought that the free acids or acid salts in the cyanoimidazolinone area might be more susceptible than their esters to breakdown in the plant and/or soil (Figure 1). A great deal of time was spent on trying to prepare the acids from various esters of cyanoimidazolinones or from the parent imidazolinones. The method which was found to be most successful is shown below.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Table VIII. Comparison of cyanoimidazolinone 44 to imidazolinone 48 at 63 g/ha postemergence

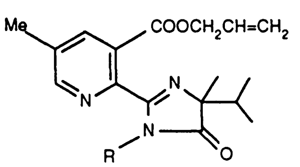


44 R = CN

48 R = H

Species	% Injury or % Control 44	48
Soybeans	11	61
Corn	22	40
Wheat	11	6
Velvetleaf	89	89
Ragweed	67	51
Wild Mustard	100	89
Morningglory	67	48
Field Bindweed	100	94
Quackgrass	44	0
Wild Oats	22	100
Purple Nutsedge	44	73
Foxtail	100	100
Barnyardgrass	44	73

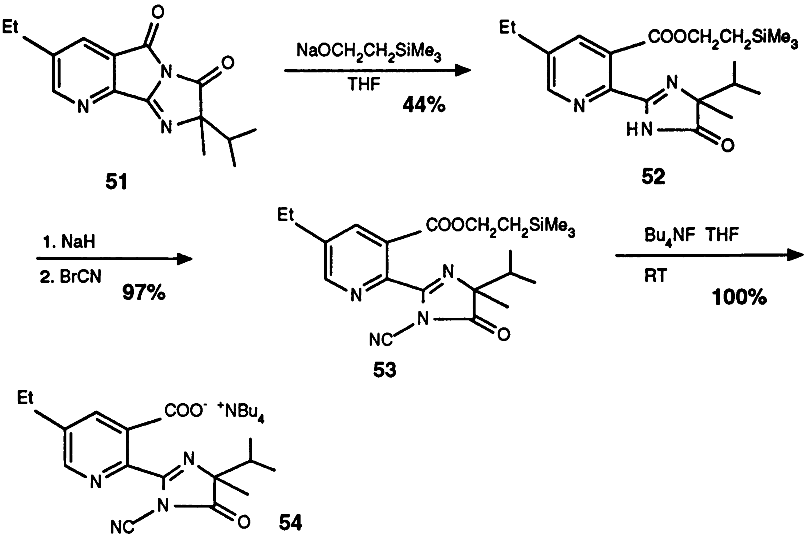
Table IX. Comparison of cyanoimidazolinone 45 to imidazolinone 49 at 32 g/ha preemergence



45 R = CN

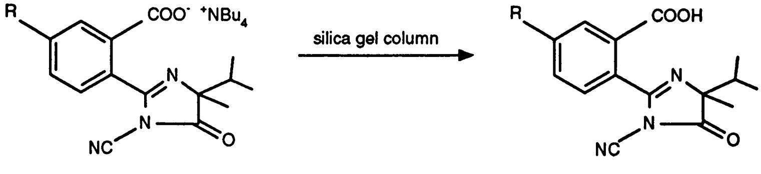
49 R = H

Species	% Injury or % Control 45	49
Corn	0	33
Velvetleaf	78	100
Ragweed	11	22
Morningglory	78	89
Field Bindweed	100	100
Quackgrass	44	89
Wild Oats	89	100
Purple Nutsedge	89	100
Foxtail	100	100
Barnyardgrass	22	100



Treatment of tricycle **51** with the sodium salt of trimethylsilylethanol afforded trimethylsilylester **52** in 44% yield after chromatography. Treatment of **52** with sodium hydride followed by cyanogen bromide afforded **53** in 97% yield. Cleavage of the trimethylsilylethyl ester was accomplished with tetrabutylammonium fluoride at room temperature, affording **54** in quantitative yield. The use of anhydrous cesium fluoride or anhydrous potassium fluoride in place of tetrabutylammonium fluoride gave no reaction.

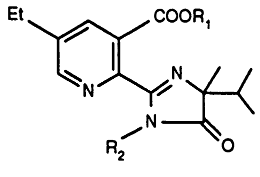
Conventional methods of dissociating tetrabutylammonium salts of carboxylic acids, such as dilute hydrochloric acid, concentrated hydrochloric acid, acidic alumina or acidic ion exchange resins failed with the cyanoimidazolinones, affording either recovered salt or decomposition. The free acids could be isolated by passing the salts through dry column silica gel packed in conventional gravity columns. The salts were also shown to dissociate to varying extents on reversed phase HPLC.



Biological Activity: Acid Salts. Table X compares cyanoimidazolinone **54** to imazethapyr **55** preemergence at 32 g/ha. Cyanoimidazolinone **54** was less effective than **55** in controlling ragweed, morningglory and foxtail but was safer on corn and showed no injury to soybeans. At 63 g/ha postemergence (Table XI), **54** was just as effective as imazethapyr in overall weed control, with the exception of wild oats, and was safer on soybeans.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Table X. Comparison of cyanoimidazolinone 54 to imazethapyr 55 at 32 g/ha preemergence

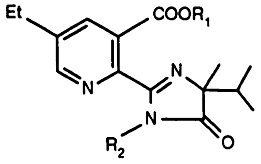


54 $R_1 = H$ $R_2 = H$

55 $R_1 = NBu_4$ $R_2 = CN$

	% Injury or % Control	
Species	54	55
Corn	11	22
Soybeans	0	0
Ragweed	0	44
Morningglory	0	89
Velvetleaf	67	89
Wild Mustard	100	100
Field Bindweed	100	100
Foxtail	22	100
Barnyardgrass	78	67
Quackgrass	89	100
Purple Nutsedge	78	100

Table XI. Comparison of cyanoimidazolinone 54 to imazethapyr 55 at 63 g/ha postemergence



54 $R_1 = H$ $R_2 = H$

55 $R_1 = NBu_4$ $R_2 = CN$

	% Injury or % Control	
Species	54	55
Soybeans	5	17
Ragweed	67	78
Morningglory	89	100
Velvetleaf	100	100
Field Bindweed	100	100
Foxtail	100	100
Barnyardgrass	100	100
Wild Oats	44	67
Purple Nutsedge	78	89

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

The free acids showed no significant advantage over their salts in terms of herbicidal activity in the greenhouse.

Cyanoimidazolinone **54** was subjected to soil persistence tests in the greenhouse in which pots which had been sprayed with **54** were reseeded with sorghum 30 days after soil application at various rates. The same was done with pots which had been treated with imazethapyr. The reseeded pots that had originally been sprayed with cyanoimidazolinone **54** showed no significant sorghum injury.

When cyanoimidazolinone **54** was applied in the field to soybeans postemergence at various rates, the weed control in the plots sprayed with **54** was significantly less than in those sprayed with imazethapyr **55**. These results suggest that **54** was undergoing facile breakdown to non-herbicidal compounds in the field too rapidly.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Conclusions

The N-hydroxyimidazolinones were synthesized via novel chemistry but did not show any significant advantage over their imidazolinone counterparts in terms of herbicidal activity or crop selectivity. The N-chloroimidazolinones showed excellent herbicidal activity in some cases, but have given no indication to date that they break down more rapidly than their parent imidazolinones to non-toxic species in the soil. The N-cyanoimidazolinones, on the other hand, showed good combinations of weed control and crop safety while showing the potential for reduced soil persistence. We have evidence that indicates that certain N-cyanoimidazolinones are less stable than their parent imidazolinones in the greenhouse and in the field.

Literature Cited

1. Los, M.; Ciarlante, D. R.; Ettinghouse E. M.; Wepplo, P. J., 184th National Meeting, American Chemical Society, **1982; PEST 21**.
2. Los, M.; Orwick, P. L.; Russell, R. K.; Wepplo, P. J., 185th National Meeting, American Chemical Society, **1983; PEST 87**.
3. Los, M., 186th National Meeting, American Chemical Society, **1983**; **PEST 65**.
4. Los, M.; *American Chemical Society Symposium Series 1984, 255*, 29-44.
5. Los, M.; Wepplo, P. J.; Russell, R. K.; Lences, B. L.; Orwick, P. L., 188th National Meeting, American Chemical Society, Philadelphia, PA, **1984**.
6. Los, M.; Wepplo, P. J.; Parker, E. M.; Hand, J. J.; Russell, R. K.; Barton, J. M.; Withers, G.; Long, D. W., 10th International Congress of Heterocyclic Chemistry, University of Waterloo, Canada, **1985**.
7. Guaciaro, M. A.; Los, M.; Russell, R. K.; Wepplo, P. J.; Lences, B. L.; Lauro, P. L.; Umeda, K.; Marc, P. A., *American Chemical Society Symposium Series* **1987**, *355*, 87-99.
8. Los, M., *Proc. Int. Congress Pesticide Chem. 6th*, **1986**, 35-42.
9. Tseng, S.-S.; Girotra, R. N.; Cribbs, C. M.; Sonntag, D. L. P.; Johnson, J. J., *American Chemical Society Symposium Series* **1991**, *443*, 122-132.
10. Los, M. U.S. Patent 4 188 187, 1980.
11. Los, M. U.S. Patent 4 297 128, 1981.

12. Los, M. Eur. Patent 41 623, 1981.
13. Los, M. Eur. Patent 133,310, 1985.
14. Los, M. Eur. Patent 133,311, 1985.
15. Los, M. Eur. Patent 135,711, 1985.
16. Los, M. Eur. Patent 158,000, 1985.
17. Los, M. U.S. Patent 4 554 013, 1985.
18. Los, M. Eur. Patent 166 907, 1986.
19. Los, M. G.B. Patent 2 174 395, 1986.
20. Los, M.; Long, D. M.; Withers, G. P. Eur. Patent 205 879, 1986.
21. Cross, B.; Los, M.; Doehner, R. F.; Ladner, D. W.; Johnson, J. J.; Jung, M. E.; Kamhi, V. M.; Tseng, S.-S.; Finn, J. M.; Wepplo, P. J. Eur. Patent 227,932, 1987.
22. Los, M. U.S. Patent 4 911 747, 1990.
23. Guaciaro, M. A. Eur. Patent 433 655, 1991.
24. Howe, R. K.; Schleppnik, F. M., *J. Het. Chem.*, **1982,** *19,* 721.
25. Liu, K. C.; Shelton, B.; Howe, R., *J. Org. Chem.*, **1980,** *45,* 3916.
26. Chiang, Y., *J. Org. Chem.*, **1971,** *36,* 2146.
27. Peake, C. J.; Strickland, J. H., *Syn. Comm.*, **1986,** *16(7),* 763.
28. Hussein, A. Q.; El-Abadelah, M. M.; Sabri, W. S., *J. Het. Chem.,* ***1984,*** *21,* 455.

RECEIVED April 17, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch007

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch008

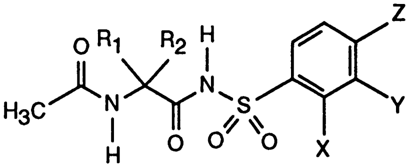
Chapter 8

Discovery of a New Class of Herbicides: Sulfonyl Carboxamides

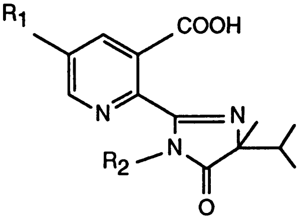
S. I. Alvarado, A. D. Crews[1], P. J. Wepplo, R. F. Doehner, T. E. Brady, D. M. Gange, and D. L. Little

**Agricultural Research Division, American Cyanamid Company,
P.O. Box 400, Princeton, NJ 08543–0400**

A potential new class of herbicides of the structural type shown below which inhibit acetohydroxy acid synthase has been discovered at the Agricultural Research Division of American Cyanamid. The Level of herbicidal activity is increased by addition of halogens to the aromatic portion of the structure while crop selectivity is improved with addition of alkyl or alkoxy groups on the aromatic moiety. A scheme of synthetic methodology as well as a description of structure activity relationships will be given.



As part of a general program aimed at the synthesis of imidazolinone analogues which are described by the generic structure below, N-sulfonation was investigated.



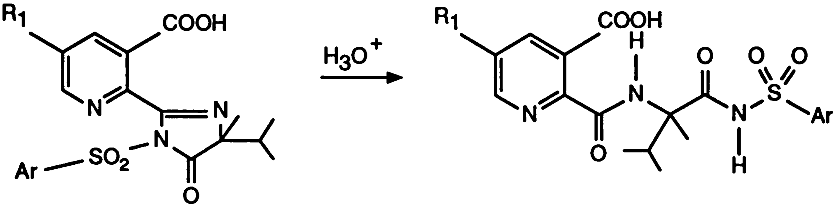
Hydrolysis of the sulfonation product afforded a diamide which exhibited excellent herbicidal activity.

---

[1] Corresponding author

0097–6156/92/0504–0075$06.00/0

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

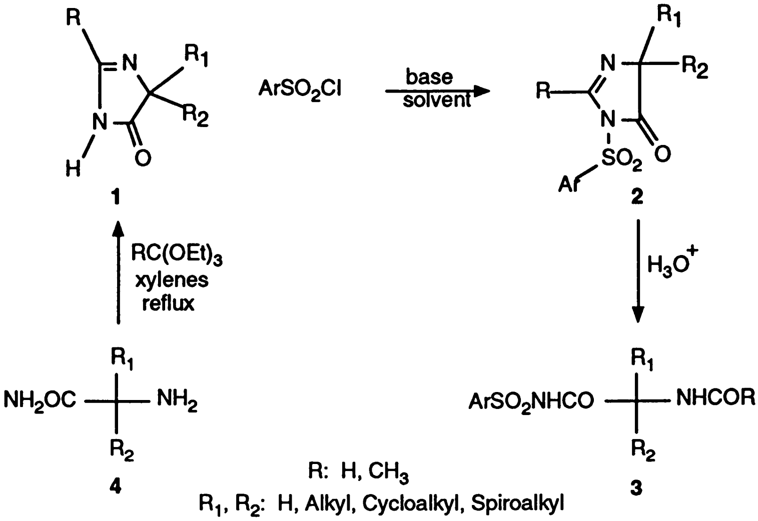

R_1
COOH
N
N
N
SO_2
Ar
O
H_3O^+
R_1
COOH
H
N
N
O
O
O O
S
N
H
Ar

The herbicidal activity was followed up with an analogue program which replaced the heterocyclic aromatic nucleus with simple alkyl groups and thus, delivered the sulfonyl carboxamides as a new class of AHAS inhibiting herbicides (*1, 2*).

Preparation of Sulfonyl Carboxamides

Sulfonyl carboxamides are prepared by one of the five general methods described below.

From N-arylsulfonylimidazolinones. Sulfonylations of imidazolinones **1** with arylsulfonyl chlorides (Scheme I) were performed using pyridine, sodium hydride or triethylamine, in methylene chloride, tetrahydrofuran or a mixture of both. The reactions were usually performed at room temperature, but in some instances were carried out at reflux, and generally required 6 to 18 hours to complete. The intermediates **2** were generally not isolated or purified, but were hydrolyzed directly to N-acylsulfonylcarboxamides **3** by treatment with dilute HCl(aq). However, intermediates **2** could be easily isolated when sodium hydride was employed as a base. Generally the hydrolysis of **2** required only a few minutes at room temperature to afford the desired products **3**, which typically could be purified by crystallization from ethanol/water or methylene chloride/hexanes.


R
N
R_1
N
R_2
H
O
1
$ArSO_2Cl$
base
solvent
R_1
N
R_2
R
N
SO_2
O
Ar
2
$RC(OEt)_3$
xylenes
reflux
H_3O^+
R_1
NH_2OC
NH_2
R_2
4
R_1
$ArSO_2NHCO$
NHCOR
R_2
3
R: H, CH_3
R_1, R_2: H, Alkyl, Cycloalkyl, Spiroalkyl

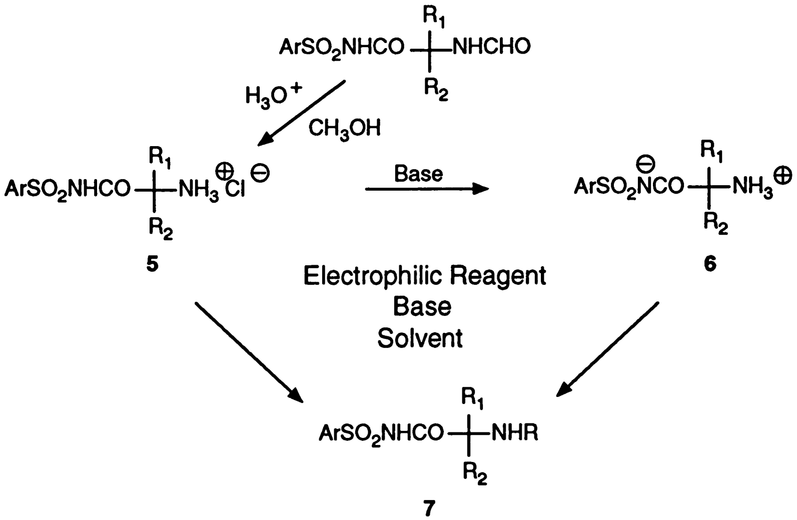
Scheme I

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch008

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch008

Imidazolinones of type **1** were prepared by reaction between aminoamides **4** and triethylorthoformate or triethylorthoacetate (Scheme I). This method was used to prepare a major protion of the carboxamides studied in this effort.

From α-Aminosulfonylcarboxamides. A second general method for preparation of sulfonylcarboxamides (Scheme II) involved reaction of amine salts **5**, or the corresponding zwitterions **6**, and electrophilic reagents. This reaction was carried out with acid chlorides, carboxylic acid anhydrides, alkyl or arylisocyanates, arylsulfonylisocyanates, and arylsulfonyl chlorides. In general, the reaction outlined in Scheme II was carried out by the addition of a base to a solution of compound **5** or **6** in a suitable solvent, followed by the addition of an electrophilic reagent.

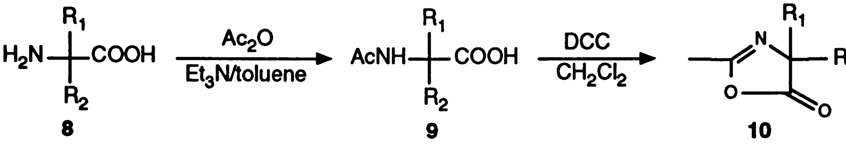

ArSO2NHCO–C(R1)(R2)–NHCHO
H3O+
CH3OH
ArSO2NHCO–C(R1)(R2)–NH3 Cl
5
Base
ArSO2NCO–C(R1)(R2)–NH3
6
Electrophilic Reagent
Base
Solvent
ArSO2NHCO–C(R1)(R2)–NHR
7

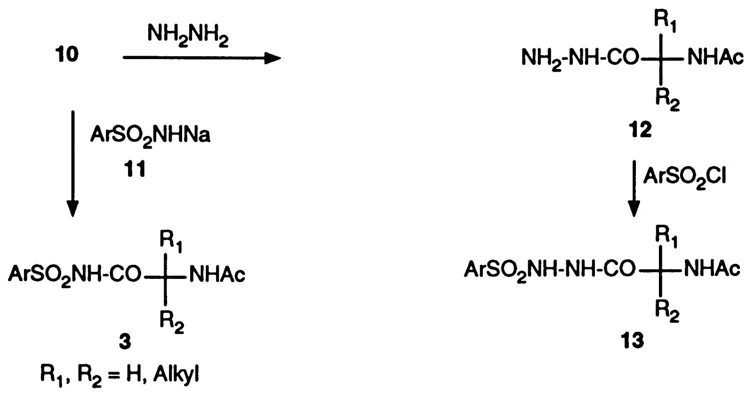
Ar = Substituted phenyl, 8-quinolinyl

Electrophilic Reagents = R-COCl, R-NCO, ArNCO, $ArSO_2NCO$, $ArSO_2Cl$

Scheme II

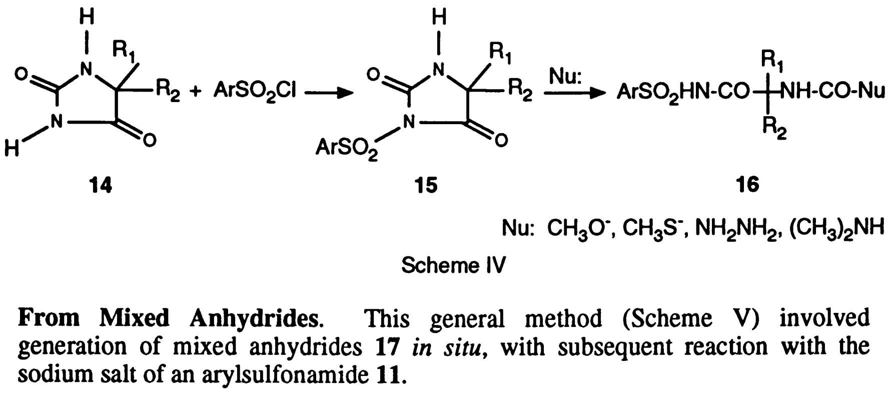
From Azlactones. Another general method for preparation of sulfonylcarboxamides **3** involved treatment of azlactones **10** (Scheme III), with arylsulfonylamide sodium salts **11**. Azlactones **10** were readily prepared from amino acids **8** via their N-acetyl derivatives **9** using standard literature procedures (*3*). Azlactones **10** also reacted with other nucleophiles, such as hydrazine, to afford hydrazides **12**, which by reaction with an arylsulfonyl chloride gave sulfonyl hydrazides **13**.


H2N–C(R1)(R2)–COOH
8
Ac2O
Et3N/toluene
AcNH–C(R1)(R2)–COOH
9
DCC
CH2Cl2
10


10
NH_2NH_2
NH_2-NH-CO-C(R_1)(R_2)-NHAc
12
$ArSO_2NHNa$
11
$ArSO_2Cl$
$ArSO_2NH$-CO-C(R_1)(R_2)-NHAc
3
$ArSO_2NH$-NH-CO-C(R_1)(R_2)-NHAc
13
R_1, R_2 = H, Alkyl

Scheme III

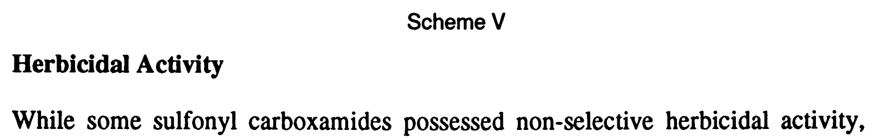
From N-arylsulfonylhydantoins. An interesting method for preparation of sulfonylcarboxamides **16** from hydantoins **14** was also developed (Scheme IV), and successfully utilized to introduce the modifications of the N-acetyl moiety indicated by reaction of intermediates **15** with nucleophiles.


14
+ $ArSO_2Cl$
15
Nu:
$ArSO_2HN$-CO-C(R_1)(R_2)-NH-CO-Nu
16

Nu: CH_3O^-, CH_3S^-, NH_2NH_2, $(CH_3)_2NH$

Scheme IV

From Mixed Anhydrides. This general method (Scheme V) involved generation of mixed anhydrides **17** *in situ*, with subsequent reaction with the sodium salt of an arylsulfonamide **11**.


AcNH-C(R_1)(R_2)-COOH
9
$ClCOOR_3$
CO-O-$COOR_3$
R_1 R_2
AcNH
17
$ArSO_2NH^-Na^+$
11
CO-NH-SO_2Ar
R_1 R_2
AcNH
3

Scheme V

Herbicidal Activity

While some sulfonyl carboxamides possessed non-selective herbicidal activity, others had selectivity in corn, wheat, barley or rice. These materials had both pre- and postemergence activity, primarily on broadleaf and composite weeds. The latter activity nicely complemented the imidazolinone weed spectrum.

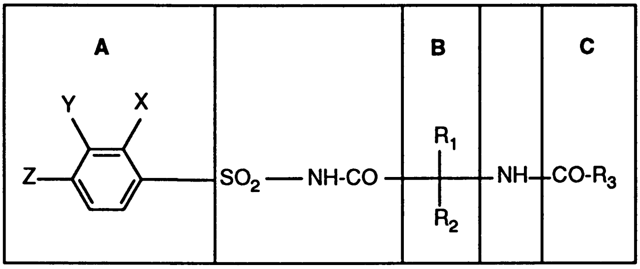
Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch008

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch008

Sulfonyl carboxamides possessing the *S* configuration were found to be solely responsible for both AHAS inhibition and herbicidal activity. The *R* isomers were totally inactive. This contrasts with the imidazolinone series, wherein the *R* isomers are 2X to 8X more active than the *S* isomers both *in vivo* and *in vitro*.

Structure-Activity Relationships

The structure-activity discussion will center on the effects of structure modification of three main regions depicted as A, B and C below.



Region A. Of phenyl substitution patterns investigated, the most interesting and active were those containing methyl, methoxy or halogen, while other substituents such as branched alkyls, benzoyl and hydroxy yielded analogues with little or no herbicidal activity. Crop safety of the active analogues was influenced by the particular aromatic substitution pattern. Halogen substitution in general enhanced herbicidal activity at the expense of crop selectivity. Alkyl substitution of the aromatic ring afforded compounds having selectivity in the small grain crops.

Region B. Of the analogues prepared, the methyl/isopropyl combination was found to be optimal for herbicidal activity. The *S* -isomer of the methyl/isopropyl combination was the active isomer both against the isolated AHAS enzyme and in whole plants, while the corresponding *R* -isomer is virtually devoid of activity.

Region C. Of the many different substitutions for the acetyl group which were made, none yielded a significant improvement in the level of biological activity. Replacement of the acetyl group with larger aliphatic acyl groups, yielded analogues with equivalent enzymatic activity, but with diminished whole plant activity. Replacement by benzoyl almost abolished the activity, while replacement by methoxycarbonyl or methylcarbamoyl maintained both enzyme and whole plant activity. However, *n*-butylcarbamoyl substitution afforded an analogue with a potent AHAS inhibitor but was inactive on the whole plant.

Conclusions

The sulfonyl carboxamides are a new class of AHAS inhibiting pre- and postemergence herbicides discovered at the Agricultural Research Division of American Cyanamid Company. Five basic methods for synthesis of the carboxamides have been defined. Structure-activity relationships which define optimum substitution patterns for crop selectivity have been determined.

Literature Cited

1. Alvarado, S. I., U.S. Patent 4,883,914, **1989**.
2. Alvarado, S. I., U.S. Patent 4,992,094, **1991**.
3. Suda, K.; Hino, F. *Chem. Pharm. Bull.*, **1985**, *33* (2), 882.

RECEIVED March 25, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch008

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009

Chapter 9

Phenyl-Substituted Five-Membered-Ring Heterocycles as Bleaching Herbicides

Frank X. Woolard

Western Research Center, ICI Americas Inc., 1200 South 47th Street, Richmond, CA 94804

Since its discovery in 1974 (*1*)the structure of fluorochloridone (**1**) has been extensively examined in the search for more active and selective bleaching herbicides. This chapter provides an overview of the work which determined the features of **1** critical for activity and structural modifications that increased its overall activity nearly ten-fold. In addition, modification of the 5-membered ring nucleus to include variously substituted imidazolidones, oxazolidines, thiazolidines, and pyrrolidines which resulted in several new series of very active bleaching herbicides is also presented.

The discovery of fluorochloridone (**1** Figure 1), the active ingredient in Racer herbicide, was made possible by an unexpected occurrence during the thermal stability testing of herbicide antidote R-25788. When heated in a sealed iron vessel at 50° for several months the sample of R-25788 slowly underwent an unprecedented (at the time) iron-catalyzed chlorine transfer cyclization reaction to form pyrrolidone R-37878. Unlike its precursor, which is herbicidally inert, R-37878 proved to be an effective pre-emergence grass herbicide which produced symptoms similar to those exhibited by the chloroacetanilides. During a subsequent synthesis program to prepare analogs of R-37878 the symptomology underwent a radical change when the allyl group on nitrogen was replaced with a phenyl ring: from chloroacetanilide-like to the strong bleaching characteristic of a carotenoid biosynthesis inhibitor. The placement of a CF_3 group at the 3-position of the phenyl ring to form **1**, carried out very soon thereafter, resulted in a substantial increase in the level of bleaching activity to where broad spectrum pre-emergence weed control could be achieved in the field at 250-300 g/ha. *In vitro* testing of **1** showed it to indeed be a strong inhibitor of phytoene desaturase, an enzyme in the carotenoid biosynthesis pathway (*2*).

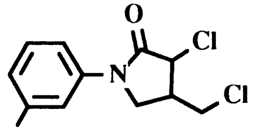
Pyrrolidones

Possessed with high levels of activity and marginal crop selectivity **1** became the focus of an ambitious effort to elucidate its structure/activity relationships (SAR) and to discover more active and/selective molecules. Since **1** is formed as a 3:1 mixture of *trans* and *cis* isomers the initial work involved chromatographic separation of the two. The more abundant *trans* isomer, whose stereochemistry was

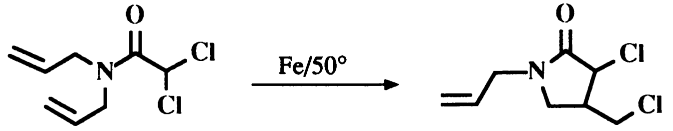
0097–6156/92/0504–0081$06.00/0

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009

proved by X-ray crystallography (*3*), was found to be approximately three-fold more active than the *cis* isomer on whole plants.



1



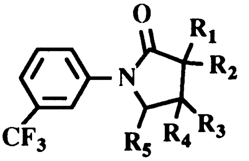
R-25788

R37878

Figure 1

The next phase involved an exhaustive exploration of phenyl ring substitution in which several hundred analogs with numerous functional groups placed at various positions were prepared. In general this showed that the 2-,4- and 6-positions of the aromatic ring could not be substituted with anything larger than a fluorine atom and although 3,5-disubstitution produced active molecules these were always less active than those with a single substituent at the 3-position. When none of the phenyl ring variants proved to be more active than **1** the synthetic effort was directed toward modifying the more challenging pyrrolidone ring.

The first variations in the pyrrolidone ring (Figure 2), achieved primarily using the copper catalyzed cyclization conditions developed by Broadhurst (*4*), demonstrated the importance of this portion of the molecule for overall activity. For example, removal of the chlorine atom at the 3-position of the pyrrolidone ring with zinc/copper couple (**2**) resulted in an approximately four-fold decrease in *in vivo* activity. The addition of a second chlorine atom or a methyl group to this position (**3** and **4**) gave similar results. Activity was lost altogether when a methyl group was added to the 4-position (**5**) and when a second chlorine was added to the chloromethyl group (**6**). If the chloromethyl group was replaced by hydrogen (**7**) all bleaching activity was also lost. The 5-position was found to tolerate no substitution at all as evidenced by the complete inactivity of **8**.



2 $R_1 = R_2 = R_3 = R_5 = H; R_4 = CH_2Cl$

3 $R_1 = R_2 = Cl, R_3 = R_5 = H, R_4 = CH_2Cl$

4 $R_1 = Cl, R_2 = CH_3, R_3 = R_5 = H, R_4 = CH_2Cl$

5 $R_1 = Cl, R_2 = R_5 = H, R_3 = CH_3, R_4 = CH_2Cl$

6 $R_1 = CH, R_2 = R_3 = R_5 = H, R_4 = CHCl_2$

7 $R_1 = Cl, R_2 = R_3 = R_4 = R_5 = H$

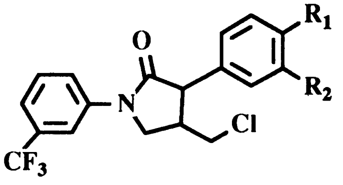
8 $R_1 = Cl, R_2 = R_3 = H, R_4 = CH_2Cl, R_5 = CH_3$

Figure 2

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009

The above observations led to the hypotheses that 1), optimum activity might depend on the presence of nucleophilic species in or near the receptor which displace one or both chlorines to covalently bind the herbicide to the protein or 2), instead of functioning as a site for covalent bond formation the chloromethyl group might just be of the proper size and lipophilicity to fit into a cleft in the protein and thus mechanically anchor the herbicide to the receptor. In the case of the chloromethyl group the available data could be used to support either nucleophilic substitution or mechanical interaction arguments. For example the 4-methyl group of 5 adds additional steric bulk which could interfere with a mechanical fit but it also makes the 4-position neopentyl, which would greatly retard nucleophilic substitution at the adjacent position. Similarly, the extra chlorine in 6 both changes the steric environment and effectively eliminates the possibility of nucleophilic substitution.

To validate or refute these ideas two key analogs were prepared in which the chlorines were replaced by groups not susceptible to displacement (Figure 3). First, the chlorine at the 3-position was replaced by a phenyl ring to give a molecule (9) that was essentially as active on whole plants as 1. A study of ring substitution on the 3-phenyl ring produced activity equivalent to fluorochloridone when the 3- and/or 4-positions were fluorinated (10). Thus *in vivo* displacement of the 3-chlorine is not required for herbicidal activity.



9 $R_1 = R_2 = H$
10 R_1, R_2 = 3-F, 4-H; 3-H, 4-F; 3,4-di-F

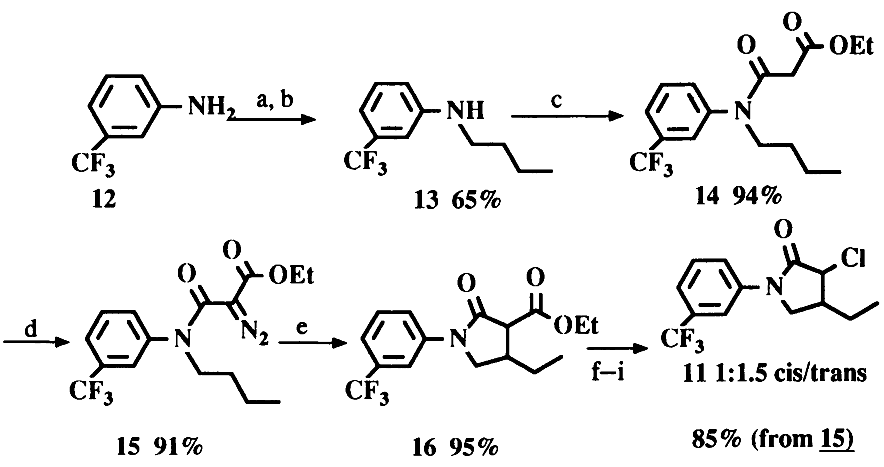
Figure 3

The possible importance of *in vivo* nucleophilic substitution at the chloromethyl group was more difficult to evaluate since the required 4-ethyl analog, 11, could not be obtained from intermediates prepared using our standard chlorine transfer cyclization procedures. Instead m-aminobenzotrifluoride (MABTF, 12) was butylated (13) and then acylated with ethyl malonyl chloride to give 14, which was then converted to diazomalonamide 15 using p-toluene sulfonyl azide (*5*). Rhodium acetate-catalyzed decomposition (*6*) of 15 formed pyrrolidone intermediate 16 which was then converted to the desired 11 by the steps shown in Figure 4.

It was expected that if nucleophilic substitution at the chloromethyl group was important for binding at the receptor site 11 should be substantially less active than 1. If, on the other hand, the chloromethyl group aids binding by purely electrostatic and/or mechanical means 11 should be as active as 1. In reality 11 is approximately 2.5 times more active and completely non-selective, strongly suggesting that the chloromethyl group provides a site for metabolism and that its contribution to substrate binding is principally electrostatic in nature.

With this new route for preparing 4-ethylpyrrolidones it became possible to prepare compounds with substituents at the 3-position that were not accessible through the chlorine transfer cyclization. For example, evidence had suggested that increasing the electron withdrawing power of the 3-substituent would increase the

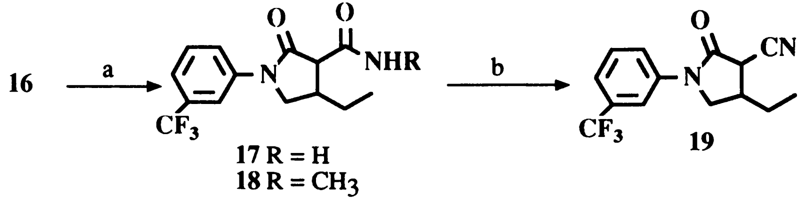
Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009



a) butyraldehyde/$TiCl_4$/TEA/PhH/Et_2O/0-3°; b) $NaBH_4$/EtOH (65%); c) ethyl malonyl chloride/PhH/0-5° (94%); d) p-TsN_3/TEA/CH_3CN (91%; e) $Rh_2(OAc)_4$/PhH/ reflux (95%); f) SO_2Cl_2/CH_2Cl_2; g) NaOH/MeOH; h) H_3O^+; i) 160° (85% from 15)

Figure 4

activity of 1 and a number of attempts were made to introduce a cyano group at this position by direct substitution methods. However, all attempts to combine cyanide ion with 1 produced only complex mixtures of unidentified products. This problem was circumvented by using the simple route shown in Figure 5 to convert 16 to cyanopyrrolidone analog 19. Unexpectedly, 19 was found to be nearly inactive at 4kg/ha while the amide precursor 17 proved to be very active. This was surprising in light of the fact that neither ester 16 nor the corresponding acid exhibit any activity at this rate. A number of analogs of 17 were then prepared which resulted in a diverse array of highly active secondary amides (7). For example 18, one of the simplest, provides non-selective pre-emergence weed control in the field at a rate of approximately 30g/ha.

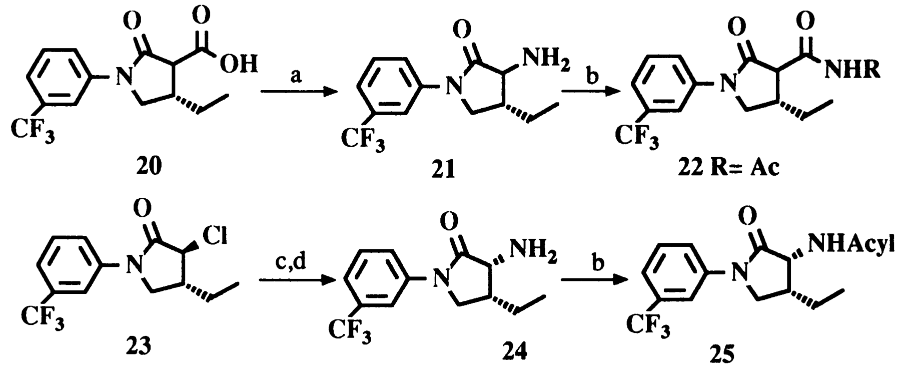


a) for 16: NH_3/MeOH (100%); for 17: CH_3NH_2/MeOH (100%); b) P_2O_5/EtOAc/reflux (73%)

Figure 5

Another series of active pyrrolidones resulted from the availability of substantial quantities of 20 and a desire to "reverse" the amide group of 18. Curtius rearrangement of *trans* 20 was smoothly accomplished by treatment with triphenylphosphoryl azide which gave *trans* 21 (Figure 6). The acylation of 21 with acetyl chloride afforded the "reversed" amide 22 which proved to be as active as 18.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009



a) Ph_3PON_3/TEA/reflux (100%); b) acylation (100%); c) NaN_3/DMF/50° (69%); d) H_2/Pd (100%)

Figure 6

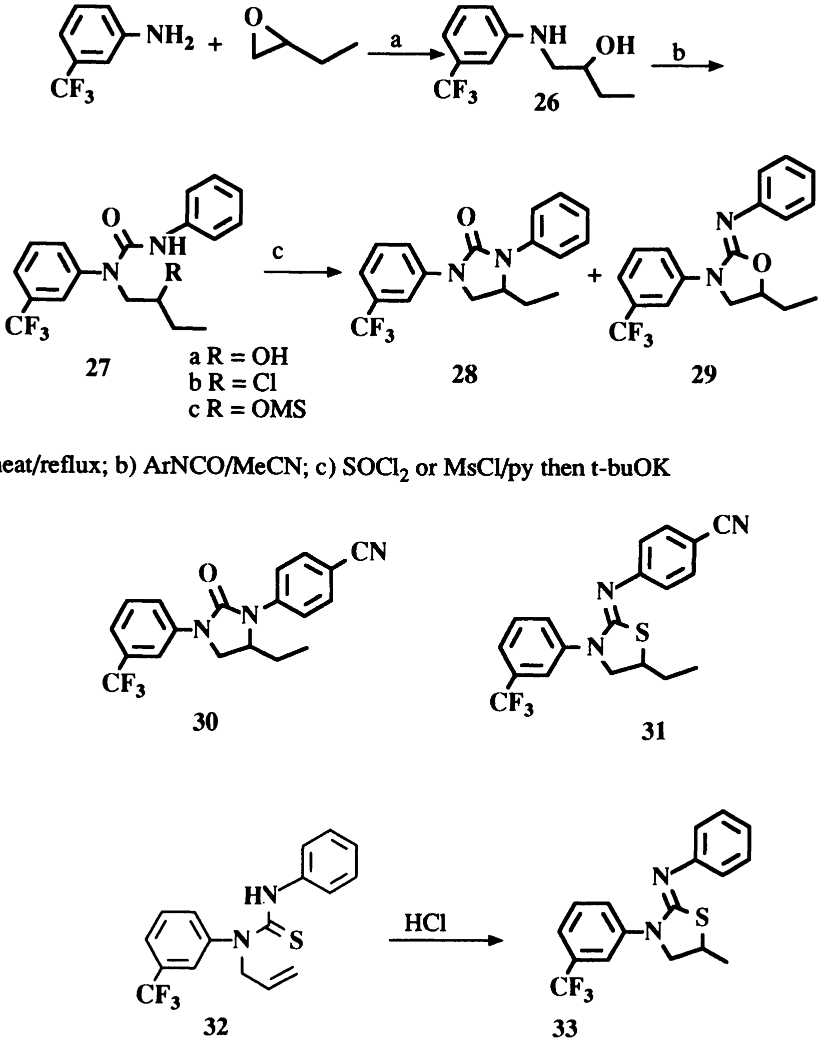
Further acylation reactions with acyl and sulfonyl halides, isocyanates, and isothiocyanates provided a number of active herbicides whose efficacy decreased with increasing size of the "acyl" group. The corresponding *cis*-isomers could be prepared by treating *trans* **11** (**23**) with sodium azide followed by reduction and acylation. Without exception these compounds were found to be three to four-fold less active than their *trans*-counterparts.

Imidazolidones and 2-Phenyliminothia(oxa)zolidines

With the knowledge that activity in the pyrrolidone series can vary greatly depending on the electronic nature of the 3-substituent it was decided to introduce an unshared pair of electrons at this position by replacing the carbon atom with a nitrogen. This was accomplished by combining anilinoalcohol **26** with phenylisocyanate and converting the hydroxyl group of the resulting urea (**27**) to an efficient leaving group by reaction with either $SOCl_2$ or mesyl chloride (Figure 7). Treatment of either **27b** or **c** with a strong, non-nucleophilic base to effect ring closure gave low yields of the desired thermodynamic product, imidazolidone **28**, and varying amounts of the kinetic product, 2-aryliminooxazolidine **29** (*8*). The two (**28** and **29**) were laboriously separated by column chromatography only to find that both were nearly inactive at 4kg/ha. Similar disappointing results were observed with imidazolidones and oxazolidines prepared from a variety of phenylisocyanates with one exception: the cyclization of the urea prepared with 4-cyanophenylisocyanate produced a poor yield of a single compound that was extremely active at 4kg/ha.

The mass spectrum of this material, which clearly showed the presence of a single sulfur atom, and irregularities in the nmr spectrum ruled out the expected structure (**30**). The identity of this new material was fixed when it was shown that the new bottle of phenylisocyanate, labeled as such by the supplier, really contained the isothiocyanate. This meant that **31**, which fit the spectral data, was the correct structure of the new active compound since sulfur would be expected to overwhelmingly dominate the ring closure reaction.

Thiazolidine **31** provided excellent pre-emergence weed control at 500g/ha and offered the potential for a new series of bleaching herbicides if an efficient synthesis of this ring system could be developed. One report in the early literature (*9*) described



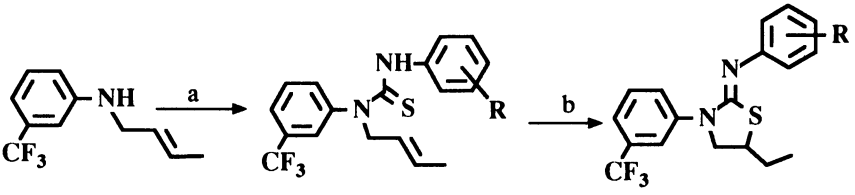
a) neat/reflux; b) ArNCO/MeCN; c) $SOCl_2$ or MsCl/py then t-buOK

Figure 7

the preparation of a phenyliminothiazolidine of this type from an allylthiourea by refluxing in concentrated HCl (32 → 33).

We found these conditions to be incompatible with sensitive functional groups and the reaction failed altogether when the allyl group was replaced by a crotyl residue. Therefore we developed the route shown in Figure 8 (*10*) which provided a variety of thiazolidines in good to excellent yields.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009



34 **35** **36**

a) PhNCS/MeCN (45-95%); b) CF_3SO_3H/MeCN/RT (65-95%)

Figure 8

As with the pyrrolidones a 3-CF_3 group was found to be the most effective substituent on the 3-phenyl ring. A study of substitution on the iminophenyl ring showed that electron withdrawing groups at the 3- and/or 4-positions provided the best activity; compound **36** (*11*) (R=4-F) in the field controls grass and broadleaf weeds pre-emergence at 250g/ha and provides complete broadleaf control post-emergence at rates as low as 15g/ha.

2-Phenyliminopyrrolidines

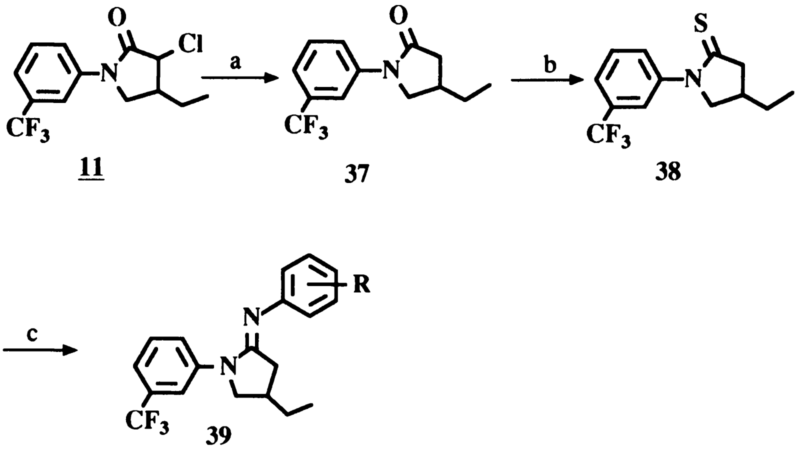
The fact that sulfur, and to some extent oxygen, could occupy the position equivalent to the 3-position of the pyrrolidone ring and provide high levels of bleaching activity led us to consider reintroducing carbon at this position. The 2-phenyliminopyrrolidines that resulted were prepared from **11** as shown in Figure 9. The yields of the final products were found to depend on the the electron withdrawing capability of the substituent(s) on the aniline and the reagent used to oxidize the thiopyrrolidone. For example, using MCPBA as the oxidant to combine **38** and aniline resulted in an 85% yield of the corresponding **39** while the reaction with 4-aminobenzonitrile proceeded in only 32% yield. The remainder of the mass balance was accounted for by the conversion of **38** back to **37** by reaction of the oxidizing thione with the carboxyl group of the oxidant. It was found that when SO_2Cl_2 was substituted for MCPBA the formation of **37** was minimized and the yields of **39** averaged 95%. The pre-emergence activity of the best of these compounds (**39**,R=4-F) in the field was slightly better than that of **1** with slightly improved cereal selectivity.

2-Acylaminothiazolidines and Pyrrolidines

Developments in another active series not discussed here pointed to the possibility that an acyl group might serve as a replacement for the phenyl ring on the imino nitrogen of the thiazolidine and pyrrolidine series. We found that the required iminothiazolidine intermediate **42** could be conveniently prepared by refluxing cyanamide **40** (*12*) and **41** in methyl ethyl ketone (MEK) in the presence of K_2CO_3 (Figure 10). Thiazolidine **42** was found to react readily with a variety of acid halides, isocyanates, isothiocyanates (*13*), and sulfonyl halides (*14*) to give a variety of herbicidally active structures (**43**). Among the most active of these **44** provides excellent post-emergence broad leaf weed control in the field at 63g/ha as well as control of many grass species.

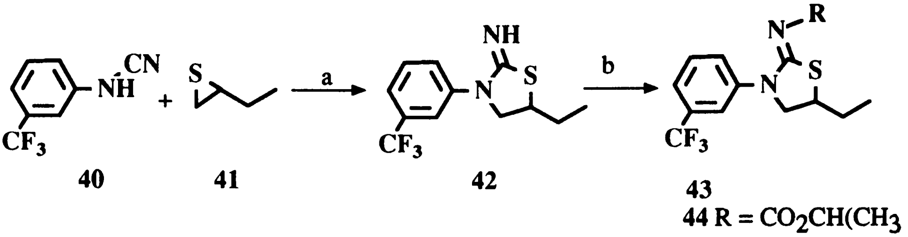
Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009



a) Zn-Cu/MeOH/reflux (100%); b) P_2S_5/THF/reflux (75%); c) MCPBA or $SO_2Cl_2/PhNH_2/CH_2Cl_2/0°$

Figure 9

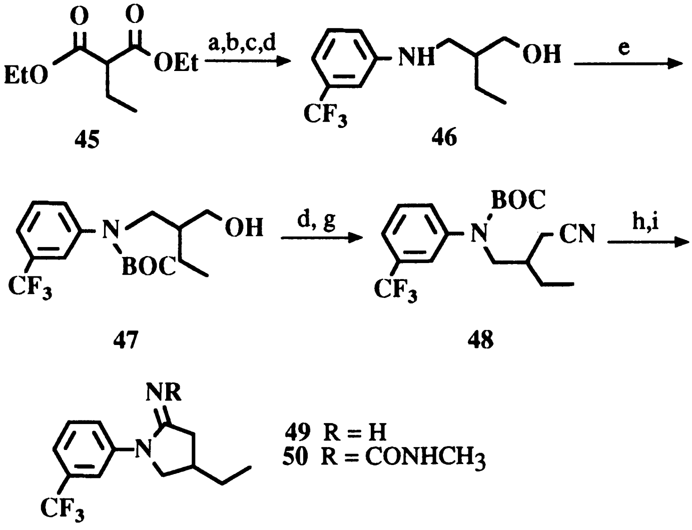


a) K_2CO_3/MEK/reflux (85%); b) acylation (85-100%)

Figure 10

The synthesis of 2-iminopyrrolidine intermediate **49** was accomplished in 47% overall yield using the standard reactions shown in Figure 11. As with **43 49** was found to react with a wide variety of acylating reagents but the substitution of the sulfur atom in the ring with carbon had a deleterious effect on the overall activity. In general the acyliminopyrrolidines were very active bleaching herbicides at rates of 1-2 kg/ha but below this level activity fell off very sharply. Compound **50** was the only exception to this and maintained acceptable levels of pre-emergence weed control at 125 g/ha.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009

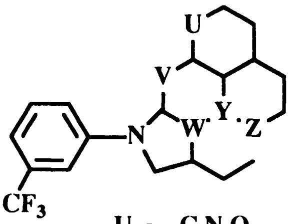


a) KOH/EtOH the HCl; b) $SOCl_2$/Ph; c) MABTF/py; d) LAH/THF (51% from 45); e) $(Boc)_2O$ (99%); f) TsCl/py; g) KCN/DMF (93%); h) HCl/Et_2O then NaOH (100%); i) acylation (90-100%)

Figure 11

Conclusion

From the preceding discussion it is clear that a substantial number of modifications can be made to the two-ring system of **1** to increase the original level of bleaching activity. When combined these various modifications define a two-dimensional structure/ activity space (Figure 12) that we have successfully used for the design of new bleaching herbicides. In general, the most active compounds in any series always contain a CF_3 group on the 3-position of the phenyl ring and an ethyl group on the position analogous to the 4-position of the pyrrolidone ring of **1**. The chlorine on the 3-position of the pyrrolidone ring in fluorochloridone can be replaced with phenyl, substituted phenyl, alkylthio, phenylthio, phenoxy, and carboxamido groups. The carbon atom at this position can be replaced by sulfur and in some limited instances by oxygen and nitrogen. Finally, the carbonyl group of **1** can be replaced by an imino nitrogen which bears either a substituted phenyl ring or a variety of acyl groups.



U = C,N,O
V = N,O,S
W = C,S,O
X = C,N,O,S
Y = C,N,O,S
Z = C,N,O

Figure 12

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch009

Acknowledgments

We wish to express our deep gratitude to those individuals who contributed greatly to this work: to Drs. Gene Teach and Ray Felix for numerous helpful discussions and profitable ideas, to Mr. Trendell Ball, Ms. Deborah Cvetic, Mr. Paul Gillespie, Ms. Lora Murray, and Mr. Jeff Springer for expert technical assistance, and to Drs. Don Bowler and Lydia Chang for spectral interpretation.

Literature Cited

1. Teach, E.G. U.S. Patent 4,069,038, 1978.
2. Lay, M.M.; Niland, A.M. *Pestic. Biochem. Physiol.* **1983**, *19*, 337-43.
3. Tseng, C.K.; Gless, R.D. Jr. *J. Org. Chem.* ***1983***, *48*, 3564-6.
4. Broadhurst, M.D. U.S. Patent 4,132,713, 1979.
5. Regitz, M.; Hocker, J.; Leidhegener, A. *Org. Syn. Coll. Vol. V.*; Baumgarten, H.E., Ed., John Wiley and Sons: New York, 1973; pp 179-183.
6. Taber, D.F.; Petty, E.H. *J. Org. Chem.* ***1982***, *47*, 4808-9.
7. Woolard, F.X. U.S. Patent 4,874,422, 1989.
8. Felix, R.A. U.S. Patent 4,900,351, 1990.
9. Dains, F.B.; Brewster, R.Q.; Blair, J.S.; Thompson, W.C. *J. Am. Chem. Soc.*, ***1922***, *44*, 2637-43.
10. Woolard, F.X. U.S. Patent 4,877,880, 1989.
11. Felix, R.A.; Springer, J.T., Teach, E.G.; Woolard, F.X. U.S. Patent 4,913,722, 1990.
12. Fauss, R., Hans, J. German Patent DE 3538128 C1, 1986.
13. Woolard, F.X. U.S. Patent 4,867,780, 1989.
14. Woolard, F.X. U.S. Patent 4,867,782, 1989.

RECEIVED June 26, 1992

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

Chapter 10

7-Phenyl-1,2,4-triazolo[1,5-*a*]pyrimidines and Related Heterocycles

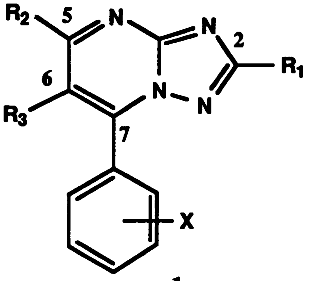
A New Family of Bleaching Herbicides

Thomas P. Selby, Tariq A. Andrea, L. Radu Denes, Bruce L. Finkelstein, Thomas P. Fuesler, and Ben K. Smith

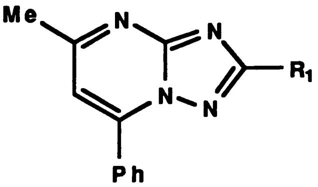
Agricultural Products, E. I. du Pont de Nemours and Company, Stine-Haskell Research Center, Newark, DE 19714

Substituted 7-phenyl-1,2,4-triazolo[1,5-a]pyrimidines and related heterocycles represent a new family of highly active herbicides which have demonstrated activity at rates as low as 31 g/ha. This class of compounds has shown broad-spectrum weed control with selectivity to key crops such as cereals, cotton, and rice. The mode-of-action was shown to be inhibition of phytoene desaturase, an enzyme involved in carotenoid biosynthesis. A summary of the discovery, synthesis, structure/activity and mode-of-action of this class of herbicides is reported.

In a continuing effort to find new heterocyclic compounds for use in agriculture, research at Du Pont has uncovered a new class of highly active herbicides represented by triazolo[1,5-a]pyrimidines of formula **1**. We discovered this herbicide class in an exploratory program initially focused on preparing phenyl-substituted triazolo[1,5-a] pyrimidines for general biological screening. Previously patented as a photographic additive *(1)*, 5-methyl-7-phenyl-1,2,4-triazolo[1,5-a]pyrimidine **2** showed very little herbicidal activity. In contrast, the closely related 2-methylthio analog **3** demonstrated an interesting level of activity and produced bleaching symptoms. This finding prompted the preparation of additional analogs. A further increase in activity was eventually obtained from a 2-trifluoromethyl derivative **4**. Consequently, an even more extensive synthesis effort followed and the key results from this work are reported here.



1



2 R_1 = H
3 R_1 = SMe
4 R_1 = CF_3

0097-6156/92/0504-0091$06.00/0

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

Chemistry

Triazolo[1,5-a]pyrimidines. Many of the phenyl-1,2,4-triazolo[1,5-a] pyrimidines reported in this paper were readily prepared via condensation of 3-amino-1,2,4-triazoles with phenyl-substituted 1,3-dicarbonyl synthons, most commonly phenyl-1,3-diketones. In addition, other analogs were made by derivatization of the substituents on these intact triazolo[1,5-a]pyrimidines.

Reaction of 3-amino-1,2,4-triazoles **5** with phenyl-1,3-diketones **6** is shown in Figure 1. Aminotriazoles **5** where R_1 is hydrogen or methylthio were commercially available and aminotriazoles **5** where R_1 is alkyl or trifluoromethyl were made by known methods *(2-4)*. Phenyl diketones **6** were readily prepared, generally by a Claisen condensation of an acetophenone with an alkyl ester. Heating aminotriazoles **5** and diketones **6** in glacial acetic acid afforded regioisomers **7** and **8** which were separated by chromatography. The predominant products **7** were usually isolated in 60-70% yield and the minor products **8** (not of herbicidal interest) in less than 10% yield. The assigned regiochemistry was in agreement with literature precedent *(5)* as well as verified by a X-ray crystal analysis in one case (**31**, *vide infra*).

Heating 3-amino-5-trifluoromethyl-1,2,4-triazole with 3-chloro-4-phenyl-2,4-butanedione or 3-methyl-4-phenyl-2,4-butanedione gave 2-trifluoromethyl-triazolo[1,5-a]pyrimidines **9** (substituted at the 6-position) as the major products (Figure 2).

Syntheses of phenyltriazolo[1,5-a]pyrimidines having no substitution or substitution other than alkyl at the 5-position are given in Figure 3. Reaction of *meta*-trifluoromethylacetophenone with N,N-dimethylformamide dimethyl acetal by heating neat gave enamine **10** which was then heated with 3-amino-5-trifluoromethyl-1,2,4-triazole to afford **11** regioselectively (28%, 2 steps). Benzoyl dithioketene acetal **12** *(6)* was also condensed with 3-amino-5-trifluoromethyl-1,2,4-triazole to furnish triazolo[1,5-a]pyrimidine **13** in 65% yield. Displacing the 5-methylthio group of **13** with sodium methoxide gave **14**.

Preparation of 2-halo, 2-alkoxy and 2-haloalkoxy derivatives are illustrated in Figure 4. Reaction of commercially available 3,5-diamino-1,2,4-triazole with phenyl diketone **6a** afforded 2-aminotriazolo[1,5-a]pyrimidine **15** (57%) which on diazotization in concentrated hydrochloric acid or 48% hydrobromic acid provided 2-halotriazolo[1,5-a]pyrimidines **16** in 45-55% yield . Displacement of halogen with alkoxides or haloalkoxides yielded **17**. In addition, the 2-difluoromethoxy analog **18** was also made using **17** (where R is methyl) as an intermediate. Warming in 48% hydrobromic acid resulted in dealkylation to afford a 2-triazolopyrimidinone intermediate (91%) which when treated with difluorocarbene underwent largely O-alkylation to afford **18** in 46% yield and a small amount of the herbicidally inactive N-alkylated **19** (< 5%).

Other Heterocycles. In Figures 5-7, syntheses of related heterocyclic compounds are given. Condensation of 4-amino-1,2,4-triazole with phenyl diketone **6a** furnished triazolopyridazine **20** (88%) which was alkylated with phenacyl bromide to provide the salt **21** in 88% yield (Figure 5). Ring fragmentation by heating in aqueous sodium hydroxide *(7)* gave aminopyridazine **22** (65%) which was then ring aminated with O-diphenylphosphinylhydroxylamine *(8)*. The hydroiodide salt of this aminated intermediate was then isolated and heated with trifluoroacetic anhydride to afford a 32% yield of triazolo[1,5-b]pyridazine **23**.

By this same amination and ring closure chemistry, 4-picoline was converted to triazolo[1,5-a]pyridine **24** in 45% yield (Figure 6). Lithiation of **24** and treating

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

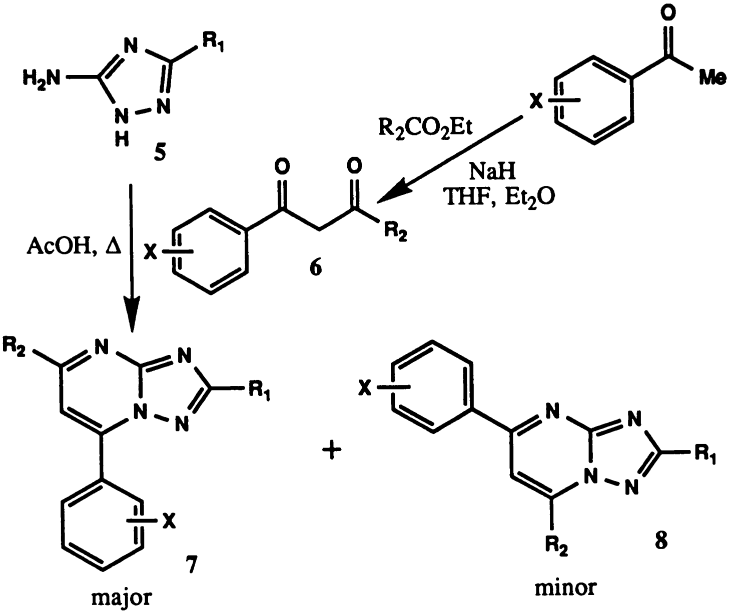

H₂N
N
R₁
N
N
H
5
R₂CO₂Et
X
O
Me
NaH
THF, Et₂O
O
O
R₂
6
AcOH, Δ
X
R₂
N
N
R₁
N
N
X
7
major
+
X
N
N
R₁
N
N
R₂
8
minor

Figure 1. Reaction of 3-Amino-1,2,4-triazoles with Phenyl-1,3-diketones.

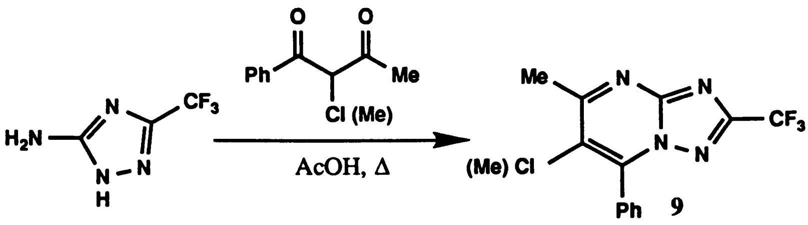

H₂N
N
CF₃
N
N
H
O
O
Ph
Me
Cl (Me)
AcOH, Δ
Me
N
N
CF₃
(Me) Cl
N
N
Ph
9

Figure 2. Preparation of 6-Substituted Triazolo[1,5-a]pyrimidines.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

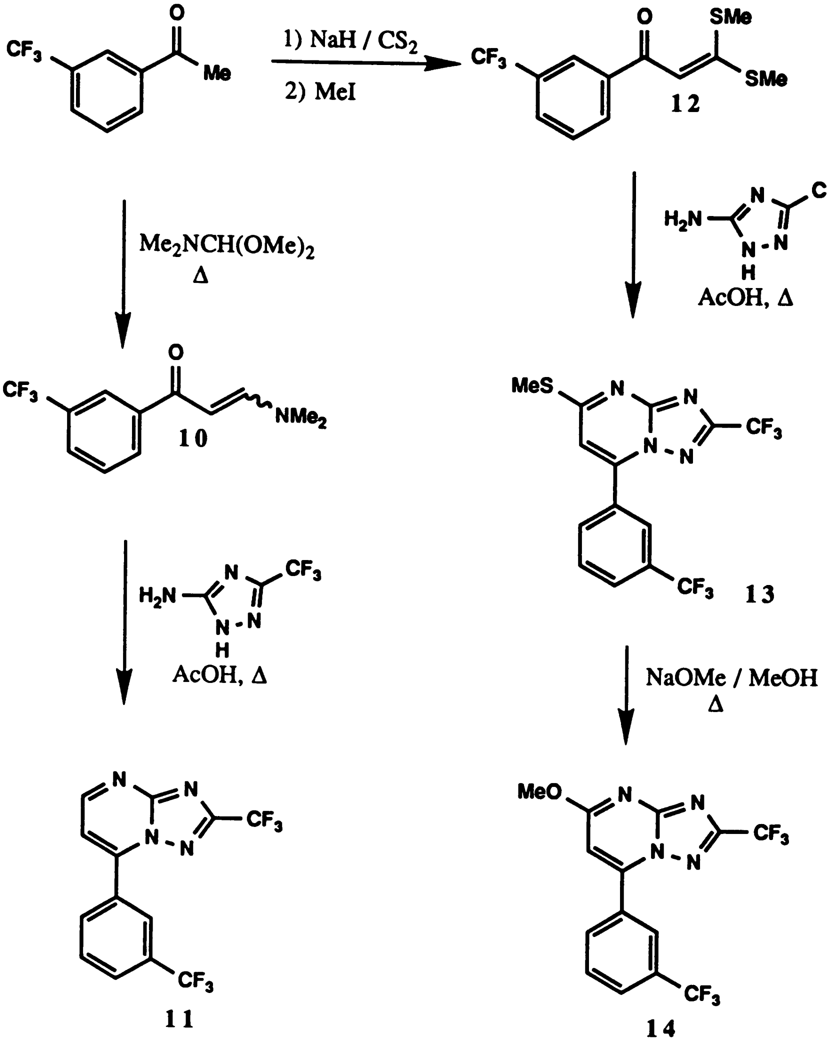

CF3
O
Me
1) NaH / CS2
2) MeI
CF3
O
SMe
SMe
12
Me2NCH(OMe)2
Δ
H2N
N
CF3
N-N
H
AcOH, Δ
CF3
O
NMe2
10
MeS
N
N
CF3
N-N
CF3
13
H2N
N
CF3
N-N
H
AcOH, Δ
NaOMe / MeOH
Δ
N
N
CF3
N-N
CF3
11
MeO
N
N
CF3
N-N
CF3
14

Figure 3. Reaction of a Benzoyl Enamine and Dithioketene Acetal with 3-Amino-5-trifluoromethyl-1,2,4-triazole.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

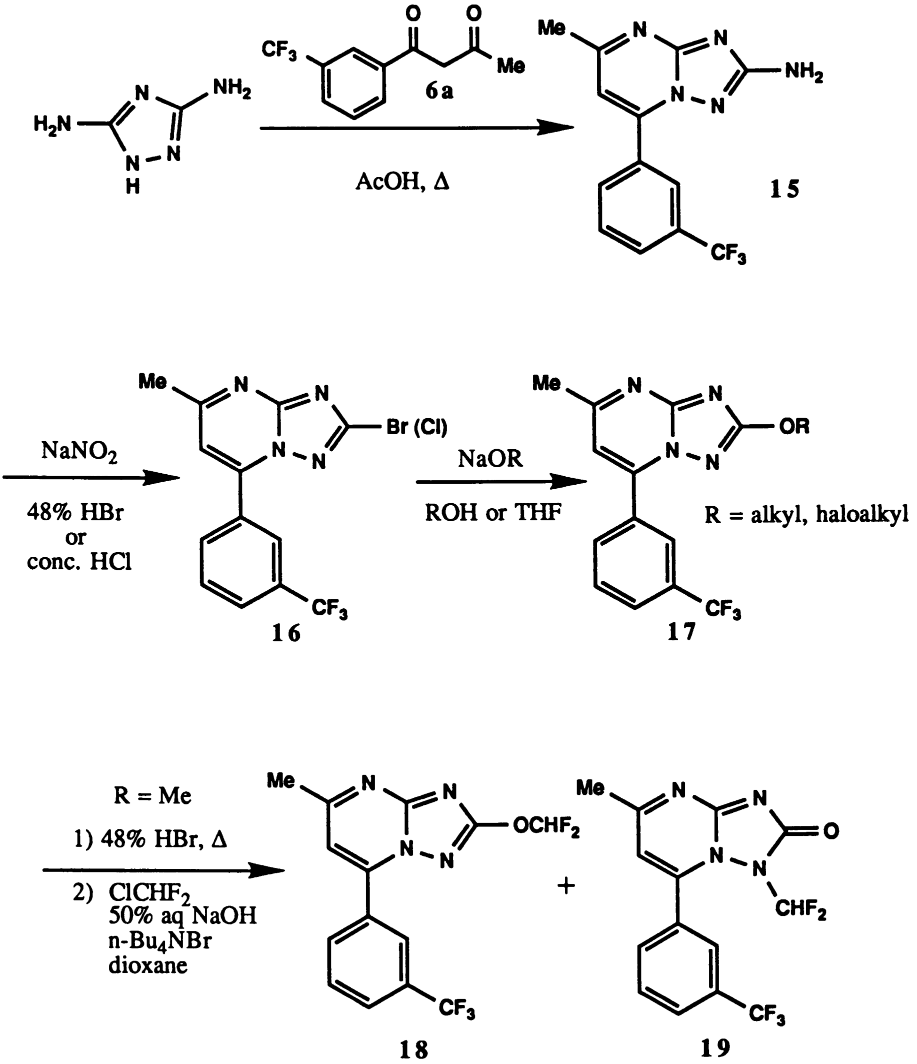

H₂N
NH₂
N
N
N
H
CF₃
O
O
Me
6a
AcOH, Δ
Me
NH₂
15
CF₃
NaNO₂
48% HBr
or
conc. HCl
Br (Cl)
16
NaOR
ROH or THF
OR
R = alkyl, haloalkyl
17
R = Me
1) 48% HBr, Δ
2) ClCHF₂
50% aq NaOH
n-Bu₄NBr
dioxane
OCHF₂
+
O
CHF₂
18
19

Figure 4. Synthesis of 2-Alkoxy and Haloalkoxytriazolo[1,5-a]pyrimidines.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

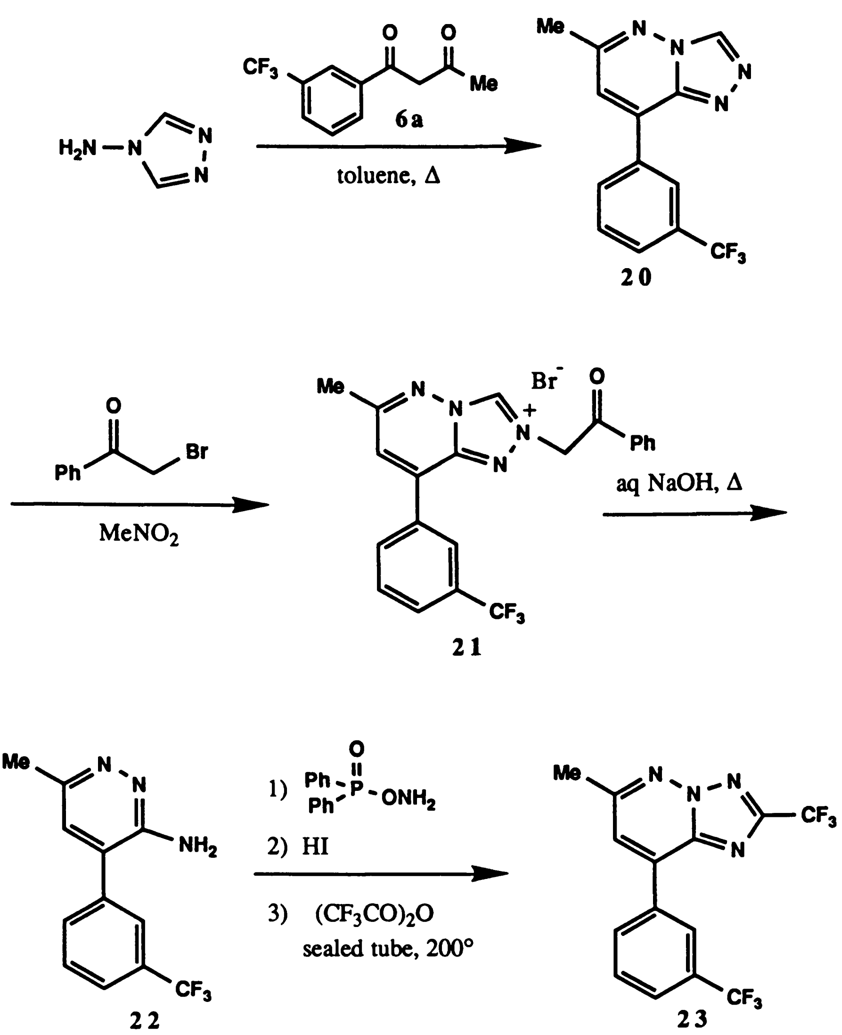

6a
toluene, Δ
20
MeNO2
21
aq NaOH, Δ
22
1) Ph2P(O)ONH2
2) HI
3) (CF3CO)2O
sealed tube, 200°
23

Figure 5. Synthesis of a Triazolo[1,5-b]pyridazine.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

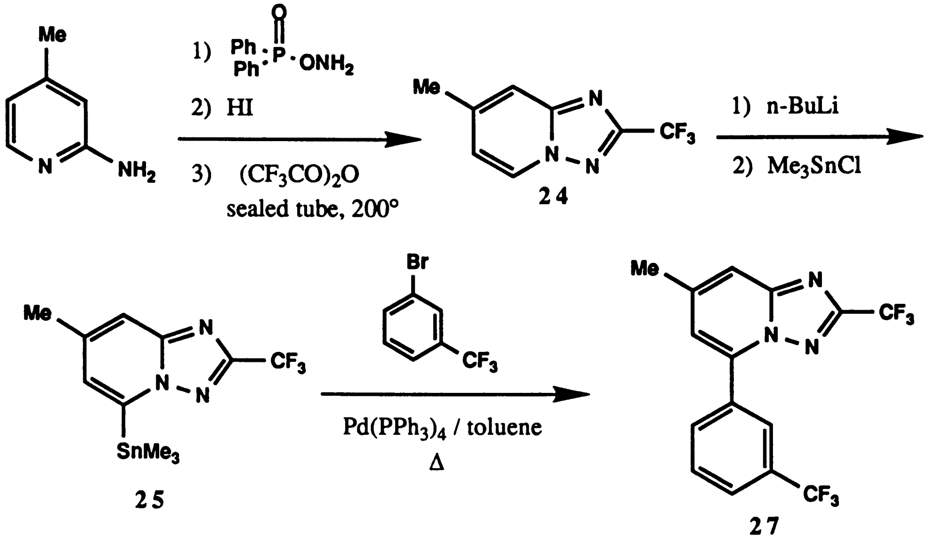

Me
NH2
N
1) Ph2P(O)ONH2
2) HI
3) (CF3CO)2O
sealed tube, 200°
Me
N
N
N
CF3
24
1) n-BuLi
2) Me3SnCl
Me
CF3
SnMe3
25
Br
CF3
Pd(PPh3)4 / toluene
Δ
Me
CF3
CF3
27

Figure 6. Synthesis of a Triazolo[1,5-a]pyridine.

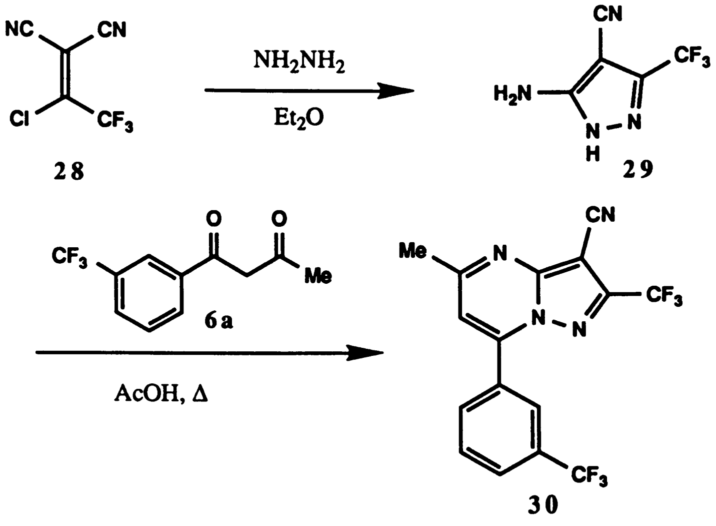

NC
CN
Cl
CF3
28
NH2NH2
Et2O
CN
CF3
H2N
N
N
H
29
CF3
O
O
Me
6a
AcOH, Δ
CN
Me
N
CF3
N
N
CF3
30

Figure 7. Synthesis of a Pyrazolo[1,5-a]pyrimidine.

with trimethyltin chloride gave stannane **25** which underwent palladium (0) catalyzed coupling with *meta*-bromobenzotrifluoride to yield **27** (57%, 2 steps).

Finally, reaction of 1,1-dicyano-2-chloro-2-trifluoromethylethylene (**28**) *(9)* with hydrazine afforded aminopyrazole **29** (Figure 7). Condensing diketone **6a** with **29** then gave the cyano substituted pyrazolo[1,5-a]pyrimidine **30** in 70% yield.

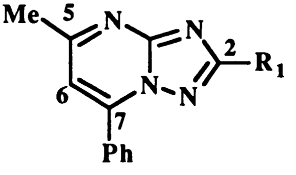
Herbicidal Results and Structure/Activity

Compounds of this family were active both preemergence and postemergence, producing bleaching symptoms. They were generally more effective when applied preemergence and demonstrated selectivity to crops including cereals, cotton, and rice. In Tables I-III, averaged preemergence herbicidal data is summarized on the following broadleaves and grasses: morning glory *(Ipomoea hederacea)*, velvetleaf *(Abutilon theophrasti)*, crabgrass *(Digitaria sanguinalis)*, giant foxtail *(Setaria faberii)*, barnyardgrass *(Echinochloa crus-galli)* and wild oats *(Avena fatua)*.

Table I provides data on 2-substituted 5-methyl-7-phenyltriazolo[1,5-a]pyrimidines at 2.0 kg/ha. A 2-trifluoromethyl group resulted in significantly higher activity than methylthio, alkyl, or hydrogen at this position. With 2-trifluoromethyl substitution, addition of a chloro or methyl group at the 6-position substantially diminished activity.

Preemergence activity at 400 g/ha for a number of 2-trifluoromethyl-7-phenyltriazolo[1,5-a]pyrimidines, with substitution varied on the phenyl ring and at the 5-position, are reported in Table II. *Meta*-substitution on the phenyl moiety was preferred over *ortho* or *para*-substitution and trifluoromethyl was found to be an optimum *meta*-substituent. Multiple substitution was also investigated but these analogs were generally less active. Small alkyl groups at the 5-position were preferred, with the following order of activity demonstrated: methyl, ethyl > *n*-propyl >> *n*-butyl, *iso*-propyl, hydrogen. Methylthio and methoxy groups at the 5-position provided diminished activity relative to 5-methyl or ethyl substitution.

Table I. Preemergence Herbicidal Activity of 2-Substituted 5-Methyl-7-Phenyltriazolo[1,5-a]pyrimidines at 2.0 kg/ha

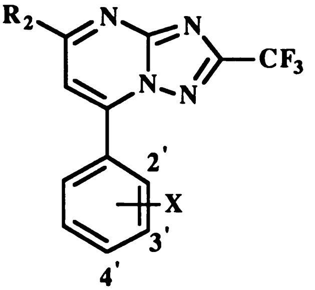
	R_1	Average % Control*
	H	<5
	Me	22
	Et	53
	SMe	72
	CF_3	95

* Broadleaves and Grasses

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

Table II. Preemergence Herbicidal Activity of Substituted 2-Trifluoromethyl-7-Phenyltriazolo[1,5-a]-pyrimidines at 400 g/ha

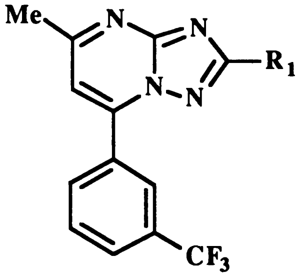
	R_2	X	Average % Control*
	Me	H	60
	Me	2'-Cl	77
	Me	3'-Cl	87
	Me	4'-Cl	<5
	Me	3'-Me	43
	Me	3'-CF_3	98
	Et	3'-CF_3	95
	n-Pr	3'-CF_3	83
	n-Bu	3'-CF_3	20
	iso-Pr	3'-CF_3	10
	H	3'-CF_3	17

* Broadleaves and Grasses

In Table III, data for 2-substituted 5-methyl-7-(*meta*-trifluoromethylphenyl)-triazolo[1,5-a]pyrimidines at 125 and 62 g/ha reveal the following order of activity: difluoromethoxy > trifluoromethyl > trifluoroethoxy > methoxy, halogen. At 31 g/ha, the best compound (where $R_1 = OCHF_2$) still controlled velvetleaf, crabgrass, barnyardgrass and giant foxtail.

Although all of these compounds demonstrated significant wheat and cotton tolerance, an increase in herbicidal activity was generally accompanied by an increase in crop phytotoxicity. However, crop safety was still sufficient to warrant field testing of some compounds.

Table III. Preemergence Herbicidal Activity of 2-Substituted-5-Methyl-7-meta-trifluoromethylphenyltriazolo[1,5-a]-pyrimidines at 125 and 62 g/ha

		Average % Control*	
	R_1	125 g/ha	62 g/ha
	CF_3	98	75
	$OCHF_2$	98	94
	OCH_2CF_3	83	68
	OMe	62	47
	Br	52	42
	Cl	72	35

* Broadleaves and Grasses

Triazolo[1,5-b]pyridazine **23**, triazolo[1,5-a]pyridine **27** and pyrazolo[1,5-a]pyrimidine **30** were all active but only **27** demonstrated a level of efficacy comparable to its triazolo[1,5-a]pyrimidine counterpart.

We used QSAR early in our analoging effort to predict preferred moieties and prioritize synthesis objectives. For example, regression analysis of crabgrass activity and 2-substitution on the triazolo[1,5-a]pyrimidine provided the equation below. Increasing lipophilicity *(π)* and electron-withdrawing capability *(F)* tended to enhance herbicidal activity whereas increasing size *(MR)* tended to reduce efficacy.

QSAR (2-Position)

Activity on Crabgrass

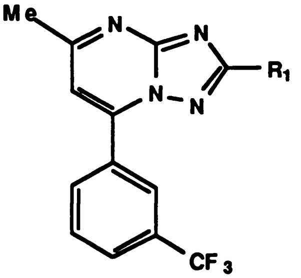
$$\log 1/GI_{50} = -0.897 + 0.573\,\pi + 2.480\,F - 0.00102\,MR^2$$

$$N = 21;\ s = 0.657;\ R = 0.755$$

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

Cereal Field Testing

We were particularly interested in compounds of this class due to their tolerance by cereal crops. Both **31** and **32** were field tested as wheat herbicides at preemergence rates of 75 - 250 g/ha. Blackgrass *(Alopecurus myosuroides)* and a number of other key grasses and broadleaves were controlled. However, these candidates were found to have very narrow crop safety margins and commercial development was not pursued. Studies suggested that soil placement played a key role in crop selectivity.



31 $R_1 = CF_3$
32 $R_1 = OCHF_2$

Mode-of-Action

Carotenoids protect chlorophyll in the photosynthetic apparatus of plants from undergoing photooxidative degradation by sunlight. Under normal conditions, light is absorbed by chlorophyll and this energy is passed on to the photosynthetic reaction centers and the electron transport chain. However, some of this energy can transform chlorophyll from the ground (singlet) state to the excited (triplet) state. One of the key functions of carotenoids is to convert unstable triplet chlorophyll back to its ground state. Triplet chlorophyll can also act as a photosensitizer passing its energy on to ground state (triplet) oxygen converting it to highly reactive singlet oxygen. Carotenoids also function to quench this high-energy oxygen species.

We found 7-phenyl[1,5-a]triazolopyrimidines to be inhibitors of phytoene desaturase, an enzyme involved in carotenoid biosynthesis (Figure 8). Evidence for this came from the observation that these compounds caused accumulation of the carotenoid biosynthetic intermediates phytoene and phytofluene in cucumber cotyledons following seed treatment. These same pigments also accumulate after seed treatment with the known phytoene desaturase inhibiting herbicides fluridone and norflurazon. Also, these compounds caused an accumulation of ^{14}C-phytoene with a concomitant decrease of ^{14}C-β-carotene when ^{14}C-isopentenyl pyrophosphate was used as substrate in a cell-free carotenoid biosynthesis preparation. This again demonstrated that phytoene desaturase was inhibited.

With reduced carotenoid levels, the herbicidal effect of these compounds results from subsequent photooxidative damage of chlorophyll followed by chloroplast destruction. Loss of carotenoid and chlorophyll pigments results in the characteristic bleached appearance of the treated plants.

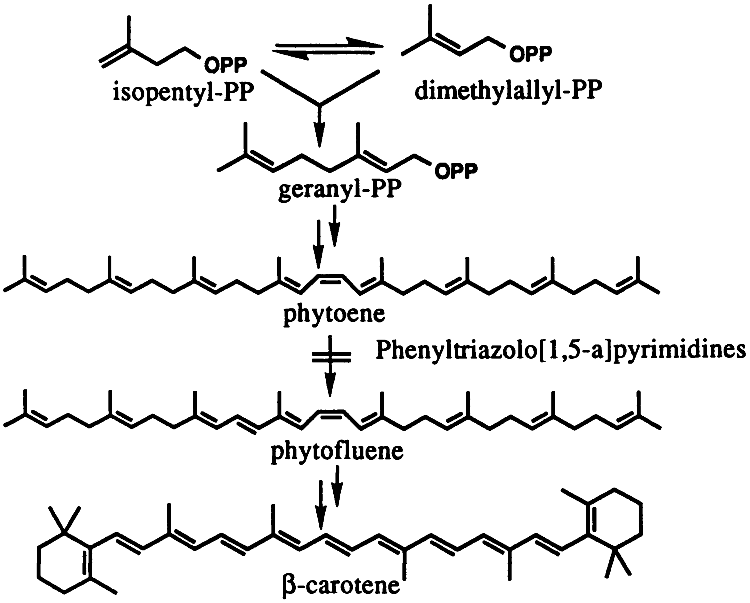


Figure 8. Inhibition of Carotenoid Biosynthesis by Phenyltriazolo[1,5-a]-pyrimidines.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

Conclusion

We have reported in this paper syntheses of a number of novel substituted 7-phenyl-1,2,4-triazolo[1,5-a]pyrimidines and related heterocycles. These compounds represent a new class of highly active herbicides, which produce bleaching symptoms. Broad-spectrum activity on both broadleaves and grasses was observed with preemergence activity obtained at rates as low as 31 g/ha in some cases. Crop tolerance was also observed and compounds of this family were of particular interest as cereal herbicides. The mode-of-action was shown to be inhibition of phytoene desaturase, an enzyme involved in carotenoid biosynthesis.

Acknowledgments

We acknowledge with gratitude all of the biologists who conducted herbicidal evaluations on these compounds. Thanks are also due K. A. Russell, P. J. Delaney, B. A. Lockett and R. C. Benson for technical assistance and H. M. Brown, J. V. Hay and A. D. Wolf for technical advice given to this program. Finally, we express our appreciation to J. C. Calabrese (Central Research and Development, Du Pont) for the X-ray crystal analysis and to R. J. Brown for his editorial advice in the preparation of this manuscript.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch010

Literature Cited

1. Heimbach, N., U.S. Patent 2,443,136, 1948.
2. British Patent 888,686, 1962.
3. Weidinger, H.; Kranz, *J. Chem. Ber.* **1963**, *96*, 1064.
4. Lopyrev, V. A.; Rakhmatulina, T. N. *Zh. Obshch. Khim.* **1983**, *53*, 1684; *Chem. Abstr.* **1983**, *99*, 592.
5. Kleschick, W. A.; Bordner, J. *J. Heterocyclic Chem.* **1989**, *26*, 1489.
6. Kawamura, S.; Sanemitsu Y.; Hamada, T.; Yoshida, R., Eur. Pat. Appl. 87 112811, 1987.
7. Becker, H. G. O.; Böttcher, H. *Tetrahedron* **1968**, *24*, 2687.
8. Klötzer, W.; Stadlwieser, J.; Raneburger, *Org. Synth.* **1985**, *64*, 96.
9. Krokhtyak, V. I.; Il'chenko, A. Ya. *Zh. Org. Khim.* **1980**, *16*, 1694.

RECEIVED April 9, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch011

Chapter 11

Diphenylpyridines

A New Class of Herbicides

**Shinichi Kawamura[1], Tatsuhiro Hamada[1], Ryo Sato[1], Yuzuru Sanemitsu[1],
Gerhard Sandmann[2], and Peter Babczinski[3]**

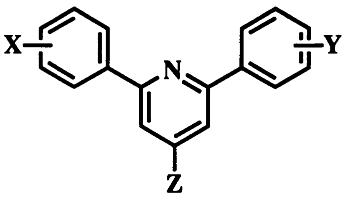
**[1]Takarazuka Research Center, Sumitomo Chemical Company Ltd.,
Takatsukasa, Takarazuka, Hyogo 665, Japan
[2]Lehrstuhl für Physiologie und Biochemie der Pflanzen, Universität
Konstanz, P.O. Box 5560, D–7750, Konstanz, Germany
[3]Agrochemical Division, Monheim Research Center, Bayer AG, D–5090
Leverkusen, Germany**

A novel series of 4-substituted 2,6-diphenylpyridines was synthesized and found to possess bleaching herbicidal activity. These diphenylpyridines, which incorporate a pyridine nucleus substituted by two phenyl moieties, are new chemical families of bleaching herbicides. The structure-activity relationships indicated very specific structure requirements for herbicidal activity. In general, herbicidal activity was the highest in compounds that contain three substituents: a CF_3 at the 2- or 3- position of one phenyl ring, a CF_3 group at the 4-position of the other, and a methoxy, ethoxy, or methylthio group at the pyridine 4-position. Physiological and biochemical properties of diphenylpyridines have been also investigated. Their primary mode of action is direct inhibition of phytoene desaturase which results in decreased biosynthesis of colored carotenoides and subsequent photooxidation of chlorophyll in the light.

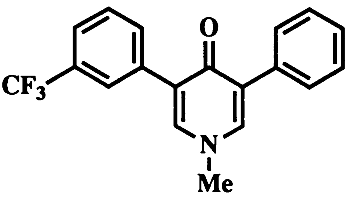
A variety of pyridines are known to possess herbicidal activity. However, only a few heterocycles with a pyridine nucleus have been reported as bleaching herbicides (*1*-*2*). Recently, a series of herbicidal pyridine derivatives was disclosed (*3*). In our continuous effort to find a new class of bleaching herbicides, we discovered that 2,6-diphenylpyridines (General Structure 1) showed bleaching herbicidal activity. In general, diphenylpyridines exhibit moderate preemergent herbicidal activity and good postemergent herbicidal activity on broadleaf weeds. At postemergent application, the chlorotic symptoms can not be observed in primary leaves, only secondary and later leaves become chlorotic, 2-3 days after application. The bleaching symptoms observed resulted in sever necrosis, leading to plant death after 25-30 days. From the symptoms and structural similarity to other well known bleaching herbicides, like fluridone and flurtamone, the compound was expected to inhibit carotenoid biosynthesis. Our interest in the structure and herbicidal activity of this novel heterocyclic compound prompted us to examine a systematic screening study on diphenylpyridine herbicides. Here, we now report the syntheses, structure-activity relationships, and mode of action of diphenylpyridines.

0097–6156/92/0504–0103$06.00/0

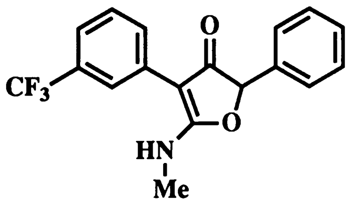
In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.



General Structure 1



fluridone



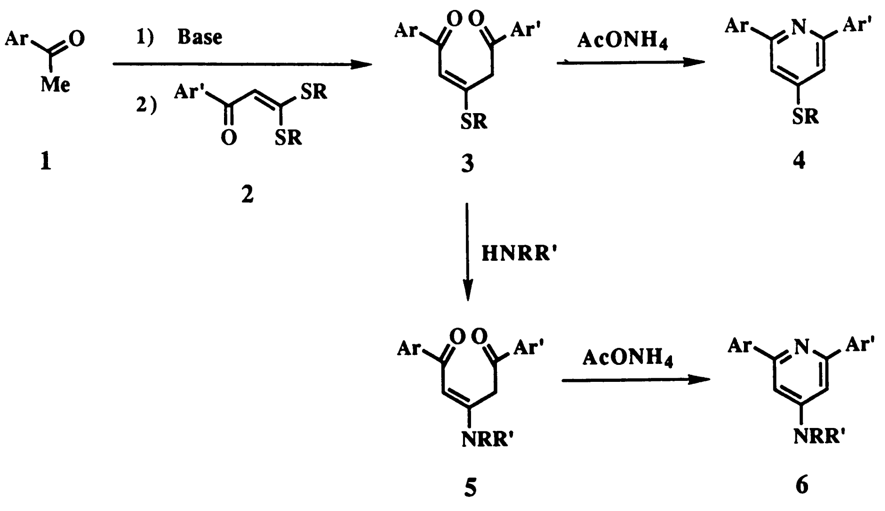
flurtamone

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch011

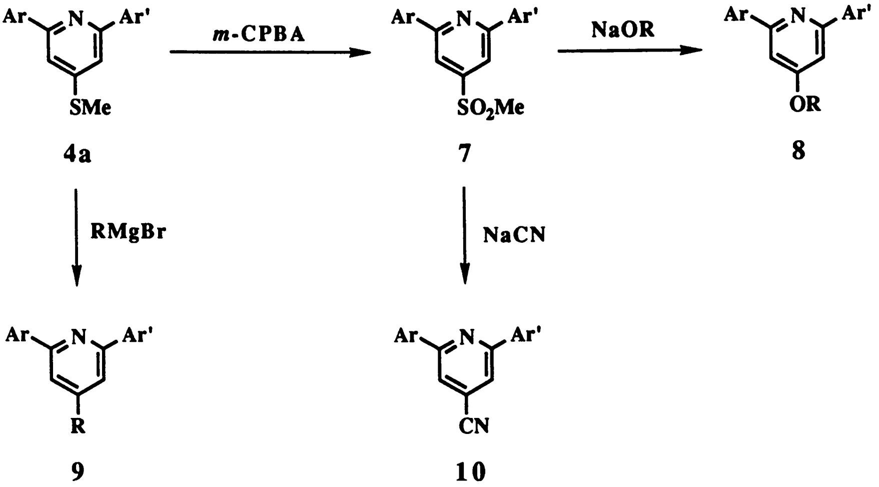
Synthesis. 2,6-Diphenyl-4-(alkylthio)pyridines **4** were synthesized in two steps from ketenedithioacetal derivatives **2**, which were prepared by the reaction of acetophenones with carbon disulfide followed by treatment with alkyl halides(*4*). Treatment of **1** with **2** afforded pentenedione derivatives **3**. Successively, cyclization of **3** with ammonium acetate yielded the 2,6-diphenyl-4-(alkylthio)pyridines **4**. The corresponding 4-amino derivatives **6** were prepared starting from **3**. Aminolysis of **3** gave 3-amino dione derivatives **5**, which were treated with ammonium acetate to afford 4-amino derivatives **6** (Scheme 1). 4-methylthio derivative **4a** was the key intermediates for preparing some 4-substituted 2,6-diphenylpyridines. The conversions of methylthio derivatives **4a** to the corresponding alkoxy **8**, alkyl **9**, and cyano **10** derivatives were achieved by a process through a nucleophilic displacement. Namely, 4-alkyl derivatives **9** were synthesized by the reaction of **4a** and alkyl Grignard reagents. Also, treatment of with *m*-chloroperbenzoic acid gave 4-methane sulfonyl derivatives **7**. 4-methanesulfonyl derivatives **7** were converted to 4-alkoxy derivatives **8** or 4-cyano derivatives **10** by treatment with sodium alkoxides or sodium cyanide as exemplified in Scheme 2.

Biology test method. The pre and postemergent herbicide evaluations were conducted on all target compounds from the series mentioned above. The test species included in these evaluations were cleavers (*Galium aparine*), common chickweed (*Stellaria media*), field pansy (*Viola arvensis*), Persian speedwell (*Veronica persica*), rounded chamomile (*Matricaria matricarioides*), field pennycress (*Thlaspi arvense*), Japanese millet (*Echinochloa frumentacea*), velvetleaf (*Abutilon theophrasti*), and morning glory (*Ipomoea purpurea*). In the preemergent tests, seeds of the test vegetation were planted. A designed amount of the test compound formulated in an emulsifiable concentrate was diluted with water and the dilution was sprayed onto the soil surface. Twenty days after treatment, the herbicidal effect and phtotoxicity were observed in comparison with untreated controls. In the postemergent tests, the developing plants (1-4 leaf stage) were subjected to foliage treatment using a small

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch011


1) Base
2)
1
2
3
4
AcONH4
HNRR'
5
6
AcONH4

Scheme 1


4a
m-CPBA
7
NaOR
8
RMgBr
9
NaCN
10

Scheme 2

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch011

sprayer with a dilute liquid containing a prescribed amount of sample emulsifiable concentrate. Twenty days after treatment, the herbicidal effect and phtotoxicity were observed in comparison with untreated controls.

Structure-Activity Relationships. To examine the structure-activity relationships, we synthesized a variety of diphenylpyridines in this study. First, we synthesized the diphenylpyridines that possess one substituent. We varied the nature and positions of the substituent, in order to examine their effects on herbicidal activity. Herbicidal activities of substituted diphenylpyridines are summarized in Figure 1. The data shows that the substituents in one phenyl ring are very important for the herbicidal activity. When a trifluoromethyl group is induced in the meta or para position, the activity is greatest. Also, substitution by methyl and trifluoromethyl groups at the ortho position resulted in a sharp increase in activity. Especially, when the phenyl ring is substituted by a trifluoromethyl group, the herbicidal activity is increased irrespective of its position.

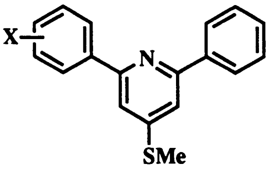
Second, diphenypyridines with one substituent in each phenyl ring were prepared, to search for the best combination of the substituent patterns in two phenyl moieties. Herbicidal activities of disubstituted diphenylpyridines are indicated in Figure 2. Two combinations of meta and para or ortho and para positions on each phenyl ring showed higher herbicidal activity than the corresponding 2-(monosubstituted)phenyl-4-methylthio-6-phenylpyridines. On the other hand, the derivatives with ortho substituents in both phenyl moieties showed reduced herbicidal activity. Also, introduction of para substituents in both phenyl rings resulted in a complete loss of activity. Other substitution patterns such as ortho and meta or meta and meta substitution appeared to have only a modest effect on herbicidal activity.

Finally, the substitution effect at the pyridine 4-position on the herbicidal activity was investigated. A variety of substituents was introduced into the pyridine nucleous of diphenylpyridines with optimum substitution in each phenyl ring (Figure 3). The substitution requirements at the pyridine 4-position were quite specific. The introduction of a methylthio, methoxy, or ethoxy group enhanced the herbicidal activity, and the methylthio derivative showed the highest herbicidal activity. On the other hand, the introduction of other substituents reduced the herbicidal activity. In the alkylthio or alkoxy group, the activities fell off rapidly with increasing length of alkyl chain.

On the basis of the limited structure-activity relationships found here, great enhancement of activity was achieved by the introduction of three substituent; an ortho or meta substituent in one phenyl ring, a para substituent in the other, and a substituent at the pyridine 4-position. One of these compounds, 2-[(3-trifluoromethyl)phenyl]-4-(methylthio)-6-[(4-trifluoromethyl)phenyl]pyridine(General Structure 1, X=m-CF_3, Y=p-CF_3, Z=SMe) showed outstanding herbicidal activity. This compound provided complete control on a large number of weed species at 63 g/ha in post emergence application, while wheat and barley were tolerant.

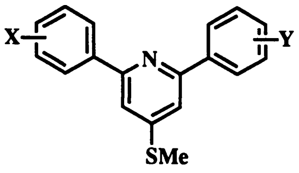
Mode of Action. The mode of action diphenylpyridines has been investigated by looking for the accumulation of metabolic intermediates in chlorotic cress leaves. As revealed by HPLC of organic leaf extracts a compound that can't be observed in controls is drastically increased. It has been identified by UV spectroscopy and HPLC co-chromatograpy with authentic phytoene. The latter has been produced by the application of the known carotenoid biosynthesis inhibitors of the tetrahydropyrimidinone type (*5*) and identified independently by UV and mass spectroscopy. A molecular ion of 544 was determined and the spectrum of this compound resembles that of 15-cis phytoene. Either with cress seedlings or cultures of the cyanobacterium *Anacystis* the decreasing effect on all other carotenoides was very similar. Xanthophylls as well as colored carotenes strongly decreased during treatment.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch011



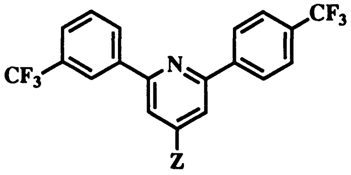
2-Me, 2-CF_3, 3-CF_3, 4-CF_3 > 3-Cl, 4-Cl >> 3-Me, 4-Me, H

Figure 1. Effect of X on Relative Herbicidal Activity



	H	ortho	meta	para
H	+	++	++	++
ortho		+	+	+++
meta			++	+++
para				-

Figure 2. Effect of Combination on Relative Herbicidal Activity



SMe, OMe, OEt > Me, NMe_2, SEt, SPr, SOMe, H

O*n*Pr, O*i*Pr, SO_2Me, NH_2, NHMe, CN, CO_2H : inactive

Figure 3. Effect of Z on Relative Herbicidal Activity

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch011

Instead, large amounts of phytoene accumulated. From these results, it can be assumed that chrorosis is caused by inhibition of carotenoid biosynthesis at the phytoene desaturase step. Loss of chlorophyll therefore should occur as a secondary effect.

In order to exclude the possibility that inhibition of phytoene desaturation is caused by indirect or regulatory mechanisms, direct interaction of substituted diphenylpyridines with phytoene desaturase was demonstrated by *in vitro* studies. Thylakoid membranes from *Anacystis* convert ^{14}C-geranylgeranyl pyrophosphate via ^{14}C-phytoene through the carotene biosynthetic pathway into ^{14}C-ß-carotene(*6*). Under our reaction conditions, accumulation of radioactivity in other carotene intermediates was negligible. Therefore, the *in vitro* synthesized ß-carotene intermediates is an indicator for the activity of phytoene desaturase. We could show the dependency of ß-carotene formation on the presence of diphenypyridines in the assay. With increasing concentrations, more phytoene is retained which means that less phytoene desaturated. Therefore less ß-carotene, the end product of this *in vitro* biosynthetic chain, is formed. Interaction of diphenylpyridines with phytoene desaturase is very similar to inhibition of this enzyme by flutamone (*7*). For the latter herbicide, it has shown that it is a reversible non-competitive inhibitor of phytoene desaturase.

Diphenylpyridines can fit into the well known pattern of diphenyl-substituted heterocycles such as fluridone, flurtamon. Common of these is a carbonyl group in the central position of heterocyclic ring. Within diphenylpyridines, carbonyl group may be replaced by a ring imine structure (C=N), which is a electronic equivalent to carbonyl group.

Conclusion. Synthesis of 2,6-diphenylpyridines have led to the discovery of a novel class of bleaching herbicides. Various structural modifications based on the parent compound resulted in the creation to 2-[(3-trifluoromethyl)phenyl]-4-(methylthio)-6-[(4-trifluoromethyl)phenyl]pyridine with potent postemergent activity. On the basis of biochemical studies, diphenylpyridines has been characterized as a new inhibitor of phytoene desaturase.

Literature Cited.

1. Martin, R. T. U.S. Patent 3249419, **1966**; *Chem. Abstr.* 1966, *65*, 4570g
2. Böger, P.; Sandmann, G. In *Target sites of Herbicide Action*; Böger, P.; Sandmann, G., Eds.; CRC Press: Boca Raton, FL, **1989**
3. Cramp, M.; Gilmour, J.; Hatton, L.; Hewett, R.; Nolan, C.; Parnell, E. *Pestic. Sci.* **1987**, *18*, 15-28
4. Potts, K. T.; Cipullo, J. M.; Ralli, P.; Theodororidis, G. *J. Org. Chem.* **1982**, *47*, 3027-3038
5. Babczinski, P.; Blunck, M.; Sandmann, G.; Schmidt, R. R.; Shiokawa, K.; Yasui, K. *Pesticide Sci.* **1990**, *30*, 339-342
6. Sandmann, G.; Kowalczyk, S. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 916-921
7. Sanmann, G.; Ward, C. E.; Lo, W. C.; Nagy, J. O.; Böger, P. *Plant Physiol.* **1990**, *94*, 476-478.

RECEIVED March 13, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Chapter 12

Structure–Activity Relationships in 3-Alkyl- and 3-Aryl-5-isothiazolylureas

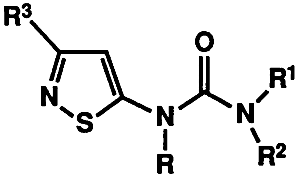
Pre- and Postemergence Herbicides with Two Possible Modes of Action

R. E. Hackler, T. W. Waldrep, and S. V. Kaster

DowElanco, 9550 North Zionsville Road, Indianapolis, IN 46268

3-(Alkyl and Aryl)-5-isothiazolylureas demonstrate both pre- and postemergent terrestrial and aquatic herbicidal activity as well as algicidal activity. The 3-alkyl compounds tend to be better as terrestrial herbicides, and the 3-aryl compounds tend to be better as aquatic herbicides and algicides. Unexpected patterns were seen in the SAR when tetrasubstituted ureas were made, and this suggested the operation of a second mode of action different than the predicted Photosystem II inhibition.

This chapter describes the structure-activity relationships in a series of isothiazoleureas **1**. These isothiazoles have an alkyl or aryl group in the 3 position (R^3), and the nature of this group has a strong effect on the activity. There is a urea group in the 5 position of the isothiazole ring, and we have observed what we consider to be some out-of-the-ordinary effects when the urea is tetrasubstituted, particularly when bulky alkyl groups are used to substitute the urea. We have not done a QSAR analysis of this series because of the possible operation of at least two modes of action, but we instead just offer our observations of the ways in which structure affects the activity.



1

Isothiazoleurea Herbicides

Isothiazoleureas are well known in the patent literature (*1-7*). They can be divided into compounds which are substituted in the four position of the isothiazole ring (*1-4*) and those which are unsubstituted in this position (*5-8*). When this position is unsubstituted, synthetic difficulties have limited which alkyl groups could be used in the 3 position. 5-Amino-3-methylisothiazole is commercially available, and patents which have a methyl group in the 3 position have issued (*5-7*)with a variety of groups on the urea portion. These compounds have good herbicidal activity. In addition, a

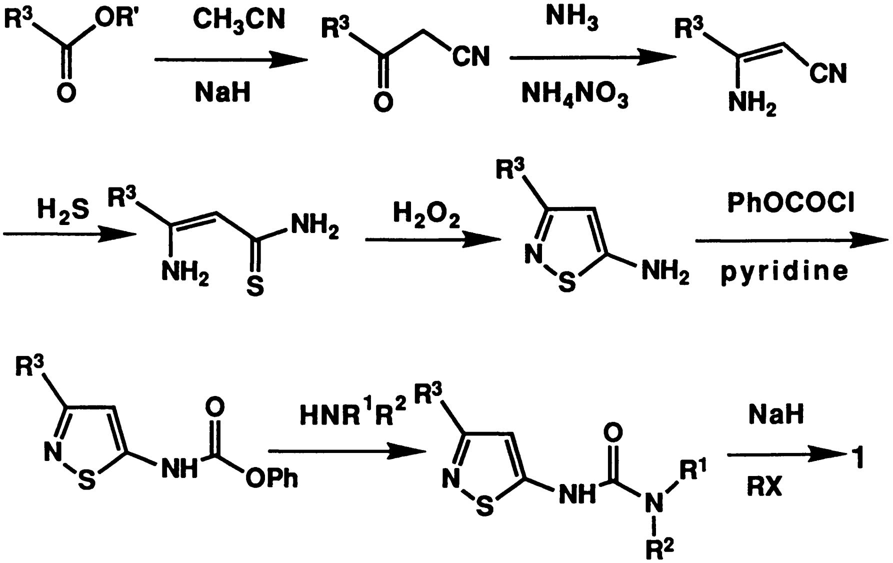
0097–6156/92/0504–0109$06.00/0

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

patent was issued with hydrogen in the 3 position (*8*). The compounds with a higher alkyl group in the 3 position are not described in these patents, and we had reason to believe from other series of ureas that these higher alkyl groups would lead to more active herbicides than the methylisothiazole ureas.

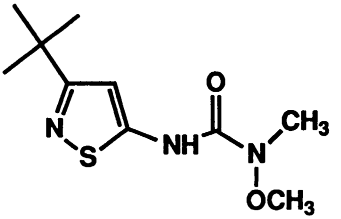
Synthetic Pathway

We have described the synthesis of the isothiazoleamines with the higher alkyl functions (*9*). The overcoming of the previous synthetic difficulties allowed the exploration of the SAR of the ureas containing these higher alkyl functions. The ureas are made from the isothiazoleamines in the typical manner. The phenyl carbamate is made using phenyl chloroformate in pyridine, and the appropriate amines are used to displace the phenol from this carbamate. The tetrasubstituted ureas are made by alkylation of the sodium salts with alkyl halides.



Unusual Structure-Activity Observations

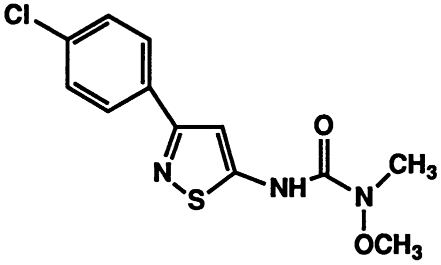
Compound 2 is a broad spectrum herbicide, and one of the most active in this isothiazole series. It demonstrates complete control of pigweed, foxtail, velvetleaf, and morningglory at 1 lb/acre both preemergence and postemergence in greenhouse studies. It controls 3 of 7 aquatic weeds at 0.5 ppm and 5 of 8 algae at 0.5 ppm.



2

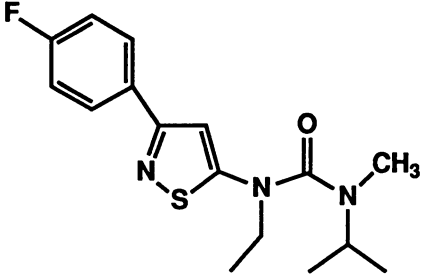
Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

When p-chlorophenyl is substituted for the t-butyl group on the isothiazole ring as in compound 3, no terrestrial herbicidal activity is observed at 8 lb/acre. This is not such an unusual observation, but what was surprising to us was that all 8 of the above-mentioned algae were controlled at 0.5 ppm, and that 4 out of 7 aquatic weeds were controlled at 0.5 ppm by compound 3. Furthermore, this was a general phenomenon - that is the aryl derivatives were not good terrestrial herbicides, but were good algicides. There are exceptions to this pattern, and these will be seen.



3

The more surprising observation is that of compound **4**, which is now a tetrasubstituted urea. In general, when ureas are tetrasubstituted, herbicidal activity is lost or greatly diminished, and the NH is thought to be important for activity in ureas and related structures(*10-13*). These tetrasubstituted isothiazoleureas seem to be an exception to this general observation. Although compound 4 is not active preemergent, it controls velvetleaf, morningglory, sicklepod, and jimsonweed at 0.5 lb/acre when applied postemergence. It is not active against aquatic weeds below 10 ppm, and controls only one of 8 algae at 0.5 ppm.



4

Mode Of Action Considerations

Compounds 2 and 3 demonstrated a strong chlorophyll fluorescence from mustard leaf discs when incubated at 3 microgram/ml for 200 min., which is indicative of PS II inhibition. Compound 4 in the same test was no different than the control, even at an elevated test level of 100 microgram/ml. There appeared to be some membrane damage at this higher level. We believe that the herbicidal activity of compound 4 is evidence for a second mode of action. Our efforts to determine this mode of action were unsuccessful. The symptomology appears to be very similar to that for PS II inhibitors, although the onset of symptoms may be somewhat quicker. The possibility of a second mode of action makes it very difficult to conduct a structure-activity analysis. Since we were unable to devise a test to measure a second mode of action, or even to be able to determine which compounds may exhibit both mechanisms, QSAR analyses had the potential of being meaningless. We believe that a second mode of action may be associated with tetrasubstitution and/or larger alkyl groups on the

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

nitrogens, although many of the tetrasubstituted derivatives were positive in the PSII biochemical assay.

Structure-Activity Relationships

The rest of this chapter will describe some of the structural changes which contribute to the relative degree of terrestrial herbicidal activity and algicidal activity. The aquatic herbicidal activity is less sensitive to these structural changes.

In Table I is seen a somewhat predictable pattern. A rate of one pound per acre was chosen because it is easier to see differences between compounds at this rate. The optimal alkyl group in this series is the t-butyl (compound **2**). The compound with the methyl (**5**) is equivalent preemergence, but less active postemergence. One can also see that some aromatic groups in this position yield active postemergent herbicides (compounds **16-18**). The phenyl and 4-fluorophenyl groups were uniformly the most active aryl groups of the ones tested, regardless of other substitution.

In Table II one can see that the effects of 3-substitution are somewhat different when one considers the N,N-dimethylureas. The t-butyl group still yields a more active compound **19** than the methyl **20**, but the optimal alkyl group now is isopropyl **22**. Aromatic groups in the 3-position **28-33** are now less active than the N-methyl, N-methoxy, a trend that appears to be related to smaller alkyl groups on the terminal nitrogen.

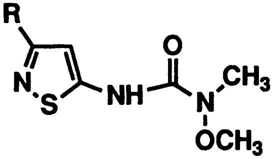
Table III shows the effects of holding the 3-substitution constant as a t-butyl, while the substitution on the urea portion of the molecule is varied. This pattern of activity is not unusual compared to other published series (*14-15*). Compound **2** is the most active compound broad-spectrum. The monomethyl derivative **35** has reduced activity, and the monoethyl compound **36** is inactive at 1 lb/acre. When one methyl group is put on the nitrogen next to the isothiazole ring and only one methyl left on the other nitrogen, it can be seen that this compound **37** is about equal to the terminal dimethyl derivative **19**. However, the tetrasubstituted derivative **44** has greatly reduced activity. In general, as the alkyl groups get larger, activity is decreased. We begin to see some of the results which were unexpected by us in the ethyl, dimethyl derivative **45**, which is virtually as active as the dimethyl compound. This compound is active in the PSII biochemical assay. Making the alkyl groups larger as in **46-48** results in greatly reduced activity.

Table IV shows many of the anomalous results which may be evidence for the operation of two modes of action. One first of all can observe in Tables I and II that the p-fluorophenyl derivatives are more herbicidally active than the corresponding p-chlorophenyl derivatives. Although compound **3** is not active at 8 lb/acre, compound **18** has good postemergent activity at 1 lb/acre. Both of these compounds are PSII inhibitors in the mustard leaf assay. When a methyl is added to the inside nitrogen of **18** to give **56**, a compound inactive at 1 lb/acre results.

Table V illustrates examples of the selectivity which occurs in this series of compounds when they are applied postemergent. Compound **2** is the most broadly active compound in the series, providing good control of three of four weeds which are problems in soybeans at one-eighth pound per acre, but also showing very high phytotoxicity to the crop. Compound 2 requires 0.5 lb/acre to completely control jimsonweed. When an isopropyl group is substituted for the methoxyl, and an isobutyl group for the t-butyl (Compound **61**), soybean tolerance is observed at one-half pound per acre, but jimsonweed control is poor. The corresponding t-butyl derivative **39** at the same rate is more toxic to soybeans and gives better jimsonweed control, but is weak on morning glory. The p-fluorophenyl derivatives are less active, and their results are shown at one pound/acre. The methyl, ethyl derivative is somewhat phytotoxic to soybeans, and is weak on morning glory, although it controls the other three weeds. Compound **4** may have the best spectrum. It is fairly tolerant to

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Table I. Effect of 3-Substitution on (5-Isothiazolyl)-N-Methoxy, N-Methyl Ureas for Premergence and Postemergence Herbicidal Activity



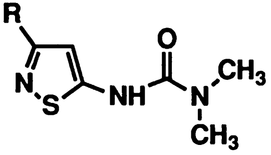
		Average Control Rating[a] at 1 lb/acre for all species[b] tested				Average Control Rating at 1 lb/acre for all species tested	
No.	R	Pre	Post	No.	R	Pre	Post
2	t-Butyl	5.0	5.0	12	1-Me,1-Et Pr	2.5	3.5
5	Methyl	5.0	3.5	13	Cyclohexyl	3.5	4.5
6	Ethyl	4.5	4.75	14	4-MeO phenyl	1.0	1.0
7	Propyl	3.5	4.25	3	4-Cl phenyl	1.0	1.0
8	Isopropyl	4.5	4.5	15	4-Me phenyl	1.0	1.0
9	n-Butyl	2.5	4.75	16	3-Me phenyl	1.75	4.0
10	sec-Butyl	5.0	4.5	17	Phenyl	3.0	4.75
11	iso-Butyl	5.0	4.75	18	4-F phenyl	1.5	4.5

[a] Rating Scale: 1 = no effect, 2 = slight effect, 3 = moderate effect, 4 = severe effect, 5 = death

[b] Species Tested: redroot pigweed, velvetleaf, morningglory, foxtail

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Table II. Effect of 3-Substitution on (5-Isothiazolyl)-N,N-Dimethyl Ureas for Preemergence and Postemergence Herbicidal Activity



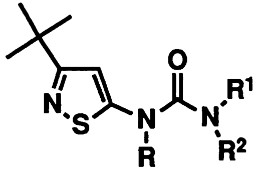
		Average Control Rating[a] at 1 lb/acre for all species[b] tested				Average Control Rating at 1 lb/acre for all species tested	
No.	R	Pre	Post	No.	R	Pre	Post
19	tert-Butyl	4.0	4.0	27	Cyclohexyl	3.75	4.0
20	Methyl	2.75	3.0	28	4-MeO phenyl	1.0	1.0
21	Propyl	3.5	3.75	29	4-Cl phenyl	1.0	1.0
22	Isopropyl	5.0	4.5	30	4-Me phenyl	1.0	1.0
23	n-Butyl	4.0	4.5	31	3-Me phenyl	1.0	1.0
24	sec-Butyl	5.0	4.25	32	Phenyl	2.75	1.0
25	iso-Butyl	4.5	4.5	33	4-F phenyl	1.0	2.25
26	1-Me,1-Et Pr	1.75	2.5	34	Benzyl	2.5	1.0

[a] Rating Scale: 1 = no effect, 2 = slight effect, 3 = moderate effect, 4 = severe effect, 5 = death

[b] Species Tested: redroot pigweed, velvetleaf, morningglory, foxtail

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Table III. Effect of Urea Substitution on (3-t-Butyl-5-Isothiazolyl) Ureas for Preemergence and Postemergence Herbicidal Activity

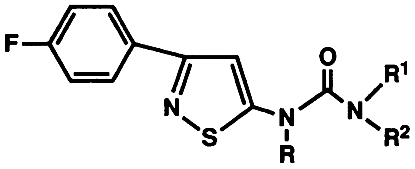


				Average Control Rating[a] at 1 lb/acre for all species[b]						Average Control Rating[a] at 1 lb/acre for all species[b]	
No.	R	R1	R2	Pre	Post	No.	R	R1	R2	Pre	Post
2	H	Me	MeO	5.0	5.0	41	H	Et	Et	3.25	3.25
19	H	Me	Me	4.0	4.0	42	H	Et	i-Pr	3.5	1.0
35	H	H	Me	3.0	3.0	43	H	Me	n-Bu	4.0	3.75
36	H	H	Et	1.0	1.0	44	Me	Me	OMe	1.5	2.75
37	Me	H	Me	4.0	3.75	45	Et	Me	Me	4.0	3.75
38	H	Me	Et	3.5	4.5	46	Et	Et	Et	1.75	1.75
39	H	Me	i-Pr	4.5	3.75	47	Et	Me	i-Pr	2.5	2.25
40	H	Me	s-Bu	4.25	2.5	48	Pr	Me	i-Pr	1.0	1.0

[a] Rating Scale: 1 = no effect, 2 = slight effect, 3 = moderate effect, 4 = severe effect, 5 = death
[b] Species Tested: redroot pigweed, velvetleaf, morningglory, foxtail

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Table IV. Effect of Urea Substitution on [3-(4-Fluorophenyl)-5-Isothiazolyl] Ureas for Preemergence and Postemergence Herbicidal Activity



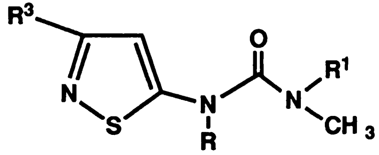
			Average Control Rating[a] at 1 lb/acre for all species[b]						Average Control Rating[a] at 1 lb/acre for all species[b]		
No.	R	R¹	R²	Pre	Post	No.	R	R¹	R²	Pre	Post
18	H	Me	MeO	1.5	4.5	55	H	Me	s-Bu	2.0	2.5
49	H	Me	Me	1.0	2.25	56	Me	Me	MeO	1.0	1.0
50	H	Me	Et	1.25	3.5	57	Et	Me	Me	1.5	3.75
51	Me	Me	Me	1.5	2.0	58	Et	Me	MeO	1.5	1.25
52	H	Me	t-Bu	1.0	1.0	59	Me	Me	i-Pr	1.0	1.0
53	H	Me	n-Bu	1.25	2.25	4	Et	Me	i-Pr	1.0	3.0
54	H	Me	i-Pr	2.75	3.0	60	i-Pr	Me	i-Pr	1.0	1.0

[a] Rating Scale: 1 = no effect, 2 = slight effect, 3 = moderate effect, 4 = severe effect, 5 = death

[b] Species Tested: redroot pigweed, velvetleaf, morningglory, foxtail

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Table V. Percent Crop Injury or Weed Control Postemergence for Some Selected 3-Substituted-5-Isothiazolyl Ureas



No.	R3	R	R1	Rate lb/acre	Soy-beans	Jimson-weed	Morning glory	Sickle-pod	Velvet-leaf
2	t-Bu	H	OMe	0.13	98	5	80	70	100
61	i-Bu	H	i-Pr	0.5	5	30	90	100	95
39	t-Bu	H	i-Pr	0.5	30	80	40	90	99
50	4-F Ph	H	Et	1.0	20	100	30	100	95
4	4-F Ph	Et	i-Pr	1.0	10	100	80	90	75
51	4-F Ph	Me	Me	1.0	5	95	100	50	50

soybeans, but provides complete control of jimsonweed, fair control of morning glory and sicklepod, and is weaker on velvetleaf. Finally, the trimethyl compound **51** is tolerated quite well by soybeans, and provides good control of jimsonweed and morning glory, but does a poor job of controlling sicklepod and velvetleaf. It is clear that the series may be manipulated in many ways to look for crop tolerance and selective control of a variety of weeds.

Algicidal Activity

Table VI demonstrates that there is much less variation in algicidal activity with variation of the 3-substituent. It seems to be a trend, however, that the aryl groups in the 3-position result in better algicidal activity, as illustrated in the table with the average rating against eight different algae. While the methyl derivative **20** is a weak algicide, the larger alkyl groups confer greater activity, and the best activity is seen with the cyclohexyl, the cyclohexylmethyl, and the aryl compounds. While phenyl and p-fluorophenyl had the best herbicidal activity among the aryl substitutents, the p-bromophenyl and the p-chlorophenyl were the preferred substituents in the algicide tests. This remained true regardless of the substituents on the nitrogens.

Table VII demonstrates that the urea tetrasubstitution does not confer greater algicidal activity as it does herbicidal activity. While compound **29** has no terrestrial herbicide activity at 8 lb/acre, compound **72** at 1 lb/acre gives ratings of 2.5 preemergence and 2.25 postemergence against the weeds of Table I. The opposite is true in the algicidal comparison of Table VII. In addition, we have previously seen that removing a terminal methyl does not greatly affect herbicidal activity, but compounds **29** and **65** show the profound effect this change produces in the algicidal activity. These differing trends in the SAR of herbicidal and algicidal activity may be further evidence of the possible operation of two modes of action.

Aquatic Herbicidal Activity

We have not listed tables of aquatic herbicidal activity because the contrasts are not so obvious in these tests. In general there is good activity against aquatic weeds across the board. The compounds in this chapter which are either good terrestrial herbicides or good algicides, also have good activity against aquatic weeds.

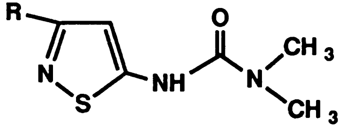
Conclusions

The isothiazoleureas described in this chapter are broadly active against aquatic weeds with a wide range of structural diversity allowed. Compounds with an alkyl group in the 3-position tend to have good terrestrial herbicidal activity, and show a typical SAR for the urea substitution. Compounds with an aryl group in the 3-position are mostly not very active against terrestrial weeds, but some compounds show good activity when they are tetrasubstituted. This activity is thought to be due to the intervention of a second, but unknown, mode of action. Compounds with an aryl group in the 3-position tend to be broadly active as algicides even when no terrestrial herbicidal activity is observed.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Table VI. Effect of 3-Substitution on (5-Isothiazolyl)-N,N-Dimethyl Ureas for Algicidal Activity



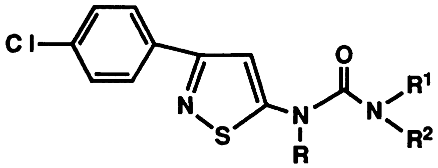
No.	R	Average Control Rating[a] at 0.5 ppm for all species[b]	No.	R	Average Control Rating[a] at 0.5 ppm for all species[b]	No.	R	Average Control Rating[a] at 0.5 ppm for all species[b]
20	Me	1.75	32	Ph	4.25	31	3-Me Ph	2.75
22	i-Pr	4.0	29	4-Cl Ph	4.88	62	4-Br Ph	4.88
19	t-Bu	3.63	33	4-F Ph	4.38	63	3-Cl Ph	3.5
24	s-Bu	3.63	28	4-OMe Ph	3.88	64	$C_6H_{11}CH_2$	4.75
27	C_6H_{11}	4.88	30	4-Me Ph	4.44			

[a] Rating Scale: 1 = no effect, 2 = slight effect, 3 = moderate effect, 4 = severe effect, 5= death

[b] Species Tested: Chlorella, Scenedesmus, Anacystis, Anabaena 1444, 1551, 1552, Chlamydomonas, Stichococcus

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Table VII. Effect of Urea Substitution on [3-(4-Chlorophenyl)-5-Isothiazolyl] Ureas for Algicidal Activity



No.	R	R1	R2	Average Control Rating[a] at 0.5 ppm for all species[b]	No.	R	R1	R2	Average Control Rating[a] at 0.5 ppm for all species[b]
3	H	Me	MeO	4.88	69	H	Me	n-Bu	4.0
29	H	Me	Me	4.88	70	H	Me	i-Pr	4.25
65	H	H	Me	1.0	71	H	Me	s-Bu	4.88
66	Me	Me	Me	2.25	72	Et	Me	Me	1.13
67	H	Me	Et	4.75	73	Et	Me	i-Pr	1.0
68	H	Et	Et	4.0					

[a] Rating Scale: 1 = no effect, 2 = slight effect, 3 = moderate effect, 4 = severe effect, 5 = death

[b] Species Tested: Chlorella, Scenedesmus, Anacystis, Anabaena 1444, 1551, and 1552, Chlamydomonas, Stichococcus

Literature Cited

1. Gibbons, L. K.; Nethery, A. A.; Ramsey, A. A., West German Patent 2,434,922, 1975; *Chem. Abstr.* **1975**, *83*, 10054y.
2. Buttimore, D., U. S. Patent 3,922,160, 1975.
3. Ramsey, A. A., U.S. Patent 4,057,415, 1977.
4. Gibbons, L. K., U. S. Patent 4,075,001, 1978.
5. Schulz, H.; Arndt, F.; Hoyer, G.-A.; Rusch, R., U.S. Patent 3,454,591, 1969.
6. Krass, D. K., U. S. Patent 4,196,126, 1980.
7. Krass, D. K., U. S. Patent 4,227,916, 1980.
8. Volpp, G. P., U. S. Patent 3,622,593, 1971.
9. Hackler, R. E.; Burow, K. W.; Kaster, S. V.; Wickiser, D. I., *J. Heterocyclic Chem.* **1989**, *26*, 1575-8.
10. Abel, A. L., *Chem. Ind. (London)*, **1957**, 1106-1112.
11. Moreland, D. E.; Hill, K. L., *J. Agric. Food Chem.*, **1959**, *7*, 832.
12. Hansch, C.; Deutsch, E. W., *Biochim. Biophys. Acta*, **1966**, *112*, 381-391.
13. Shimizu, R.; Iwamura, H.; Fujita, T., *J. Agric. Food Chem.*, **1988**, *36*, 1276-1283.
14. Kakkis, E.; Palmire, V. C.; Strong, C. D.; Bertsch, W.; Hansch, C.; Schirmer, U., *J. Agric. Food Chem.*, **1984**, *32*, 133-144.
15. Camilleri, P.; Bowyer, J. R.; Gilkerson, T.; Odell, B.; Weaver, R.C., *J. Agric. Food Chem.*, **1987**, *35*, 479-483.

RECEIVED March 30, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch012

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

Chapter 13

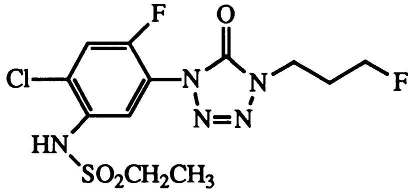
Design and Synthesis of 1-Aryl-4-substituted-1,4-dihydro-5*H*-tetrazol-5-ones

A Novel Pre- and Postemergence Class of Herbicides

George Theodoridis, Frederick W. Hotzman, Lynn W. Scherer,
Bruce A. Smith, John M. Tymonko, and Michael J. Wyle

Agricultural Chemical Group, FMC Corporation, P.O. Box 8,
Princeton, NJ 08543

1-Aryl-4-substituted-1,4-dihydro-5H-tetrazol-5-ones are a new class of membrane disrupting herbicides, which when applied pre- or post-emergence in the presence of light, control several agriculturally important weed species. The mechanism of action has been found to involve inhibition of protoporphyrinogen oxidase which then results in the build-up of a photodynamic toxicant, protoporphyrin IX. An extensive program of activity optimization resulted in the synthesis of compound **1**, a herbicide with excellent broadleaf weed control and wheat, soybean, and corn tolerance when applied preemergence and wheat and corn tolerance when applied postemergence. The synthesis, mechanism of action, and structure-activity relationship of these compounds will be discussed.



1

Comparison of the chemical structure of a number of herbicides which act as inhibitors in the electron flow of photosynthesis has shown that they all share some similarities, a nitrogen atom adjacent to a sp2 hybrid carbon N-C(=O)-. This system is bound to a lipophilic group which acts as a "carrier" (phenyl, alkyl) (*1*). It was with this concept in mind that in 1980 we initiated a synthesis program to investigate the potential as herbicides of 1-phenyl-1,4-dihydro-5H-tetrazol-5-ones (Figure 1). Early work in this area resulted in the initial lead, compound **2**, which was active in our herbicide screens at 8.0 kg/ha both pre- and postemergence.

Following further optimization of the herbicidal activity of the lead compound **2**, we soon became aware of great fluctuations in biological activity with minor changes in chemical structure. It soon became evident that neither the structural

0097–6156/92/0504–0122$06.00/0

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

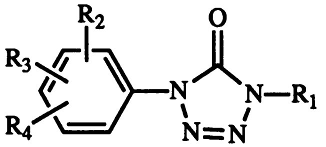

R2
O
R3
N
N—R1
R4
N=N

Figure 1. General structure of herbicides investigated.

requirements for high activity nor the whole plant symptomology of these compounds was in agreement with a photosynthesis inhibitor, and that a different mode of action was responsible for the herbicidal activity. Optimization of the initial lead led us to the discovery of compound **1** (*2,3*) (Figure 2), a herbicide that was under development consideration by the FMC Corporation. The present work will attempt to highlight the developments that led to the discovery of this highly versatile class of herbicides.

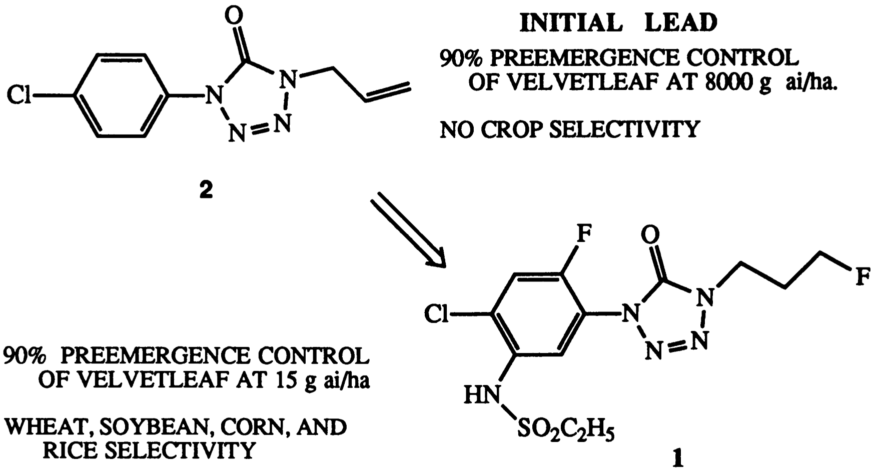

O
Cl
N
N
N=N
2
INITIAL LEAD
90% PREEMERGENCE CONTROL OF VELVETLEAF AT 8000 g ai/ha.
NO CROP SELECTIVITY
F
O
F
Cl
N
N
N=N
HN
SO2C2H5
1
90% PREEMERGENCE CONTROL OF VELVETLEAF AT 15 g ai/ha
WHEAT, SOYBEAN, CORN, AND RICE SELECTIVITY

Figure 2.

Mechanism of Action

The tetrazolinones discussed in this work act by inhibiting protoporphyrinogen oxidase (Compound **1** has a $pI_{50}=6.9$), which leads to accumulation of high levels of protoporphyrinogen IX, which in turn is spontaneously oxidized to form protoporphyrin IX. The protoporphyrin IX which cannot be readily processed by magnesium chelatase accumulates to critical concentrations (Figure 3). Sunlight leads to the formation of singlet oxygen and subsequent lipid peroxidation of the cell membrane, and eventually to cell death (*4-9*). The active tetrazolinones, when applied to the plant, produce symptoms similar to those of the diphenyl ether herbicides. Rapid onset of a "water soaking" appearance results within hours of the postemergence application of the tetrazolinone herbicide, followed by the gradual desiccation and death of the plant. When applied preemergence, the symptoms are burning of the emerging plant and desiccation.

It was also found that the tetrazolinones were effective at inhibiting the synthesis of chlorophyll in algae with a pI_{50} value for compound **1** of 5.6.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

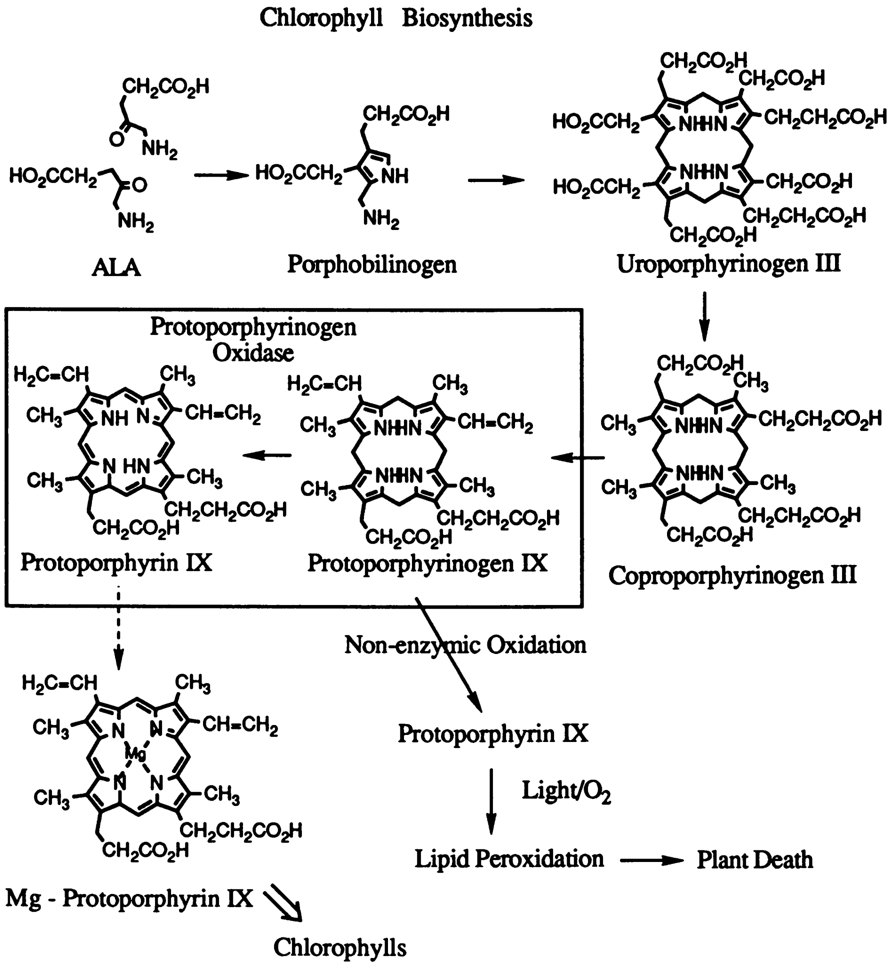

Chlorophyll Biosynthesis
ALA
Porphobilinogen
Uroporphyrinogen III
Coproporphyrinogen III
Protoporphyrinogen Oxidase
Protoporphyrinogen IX
Protoporphyrin IX
Non-enzymic Oxidation
Protoporphyrin IX
Light/O2
Lipid Peroxidation
Plant Death
Mg - Protoporphyrin IX
Chlorophylls

Figure 3. Proposed mechanism of action; inhibition of protoporphyrinogen oxidase.

Synthesis

Several reviews exist which discuss the synthesis and properties of tetrazolinones in general (*10,11*). We have previously published details on the synthesis of the tetrazolinones discussed here (*12*). In general, the initial steps involve the reaction of aryl isocyanates with a source of the azide anion. We found trimethylsilyl azide to be a safe and practical reagent which could be prepared *in situ* from trimethylsilyl chloride and sodium azide. Alkylation of the tetrazolinone ring with potassium carbonate or sodium hydride as the base in dimethylformamide and the appropriate alkyl halide gave the corresponding alkylated tetrazolinone in good yields (Figure 4).

Compounds with oxygen at the five position of the aromatic ring and alkyl groups (R_1) at the four position of the tetrazolinone ring were prepared from the reaction of the phenolic intermediate, potassium carbonate, and the corresponding alkyl halide (Figure 5).

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

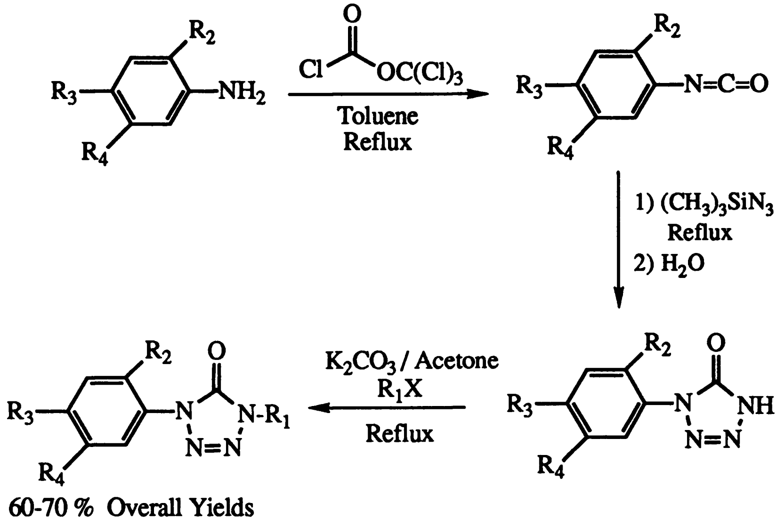

R2
R3
NH2
R4
O
Cl
OC(Cl)3
Toluene
Reflux
N=C=O
1) (CH3)3SiN3
Reflux
2) H2O
N
NH
N=N
K2CO3 / Acetone
R1X
Reflux
N-R1
60-70 % Overall Yields

Figure 4. General synthesis of tetrazolinones.

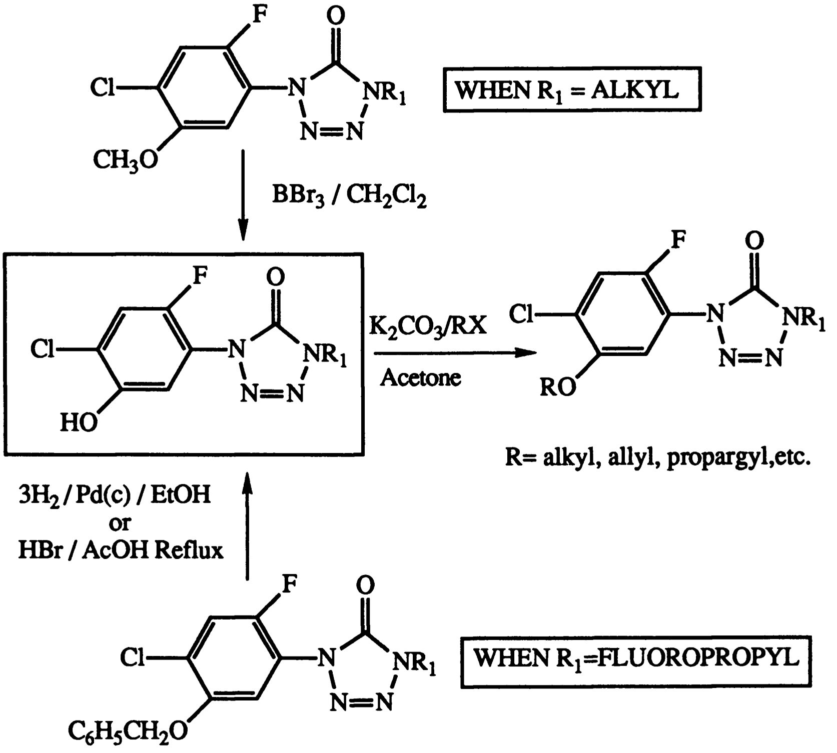

F
O
Cl
CH3O
N
NR1
N=N
WHEN R1 = ALKYL
BBr3 / CH2Cl2
HO
K2CO3/RX
Acetone
RO
R= alkyl, allyl, propargyl,etc.
3H2 / Pd(c) / EtOH
or
HBr / AcOH Reflux
C6H5CH2O
WHEN R1=FLUOROPROPYL

Figure 5. Synthesis of analogs with oxygen at the 5 position of the aromatic ring.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

The use of a benzyl group as a 5-OH protecting group proved more advantageous when R=fluoroalkyl. This protecting group could easily be removed by catalytic hydrogenation or by refluxing with 48% hydrogen bromide in glacial acetic acid for two hours. Attempts to prepare 1-(4-chloro-2-fluoro-5-hydroxyphenyl)-4-(3-fluoropropyl)-5(4H)tetrazol-5-one **4** from the treatment of the precursor **3** with boron tribromide resulted in undesirable side reactions, such as extensive replacement of the aliphatic fluorine by bromine (Figure 6).

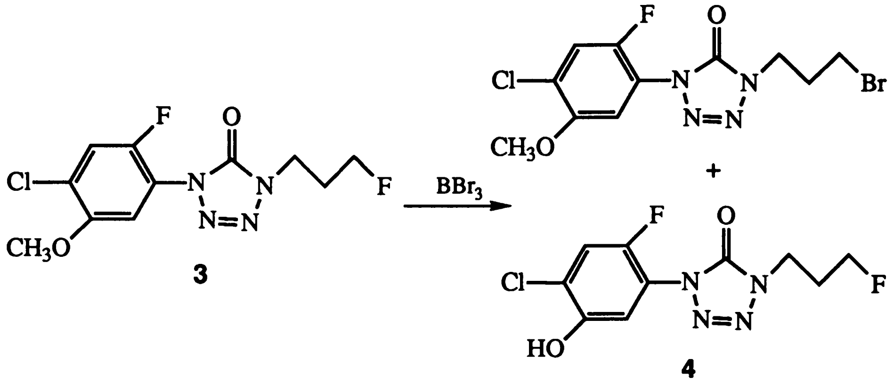


Figure 6.

Compounds with a nitrogen group at the five position of the phenyl ring were prepared, from the nitration of compound **5** with nitric acid and sulfuric acid, followed by the hydrogenation of the nitro group with PtO_2 in ethanol. Treatment of compound **7** with ethanesulfonyl chloride and pyridine gave compound **1**. When triethylamine was used in place of pyridine bis(sulfonation) predominates. Use of ethanesulfonyl chloride and triethylamine gives the bis(sulfonyl) compound **8**.

Hydrolysis of **8** with sodium hydroxide, followed by acid treatment, gives the ethanesulfonyl derivative **1** (Figure 7).

An alternative route to the synthesis of compound **1** starts with the regioselective hydrogenation of 2,4-dinitrofluorobenzene with palladium chloride and catalytic amounts of iron in glacial acetic acid (*13*). The tetrazolinone ring can be prepared in a "one pot" reaction from the *in situ* preparation of the aryl isocyanate followed by the addition of trimethylsilyl chloride and sodium azide (Figure 8).

Structure-Activity Relationships

The structure-activity relationships of these compounds has been previously published (*12*), therefore, we will only highlight some of the main features. During the early stages of the program, a variety of substitution patterns were investigated. It soon became clear that a 2,4,5-trisubstituted phenyl ring was required for optimum activity. At this point the similarities between the *in vivo* herbicidal symptomology of our compounds and that of membrane disrupter herbicides such as diphenyl ethers and oxadiazon (Ronstar®) became apparent. This led us to replace chlorine in the five position of the phenyl ring with alkoxy groups, which resulted in improved activity.

The next two breakthroughs occurred almost simultaneously. The first came about from the replacement with fluoropropyl of the allyl group at the four position of the tetrazolinone ring; this resulted in a large increase in biological activity (Figure 9). This is the first report of a fluoropropyl group having such a dramatic effect on the biological activity of a herbicide.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

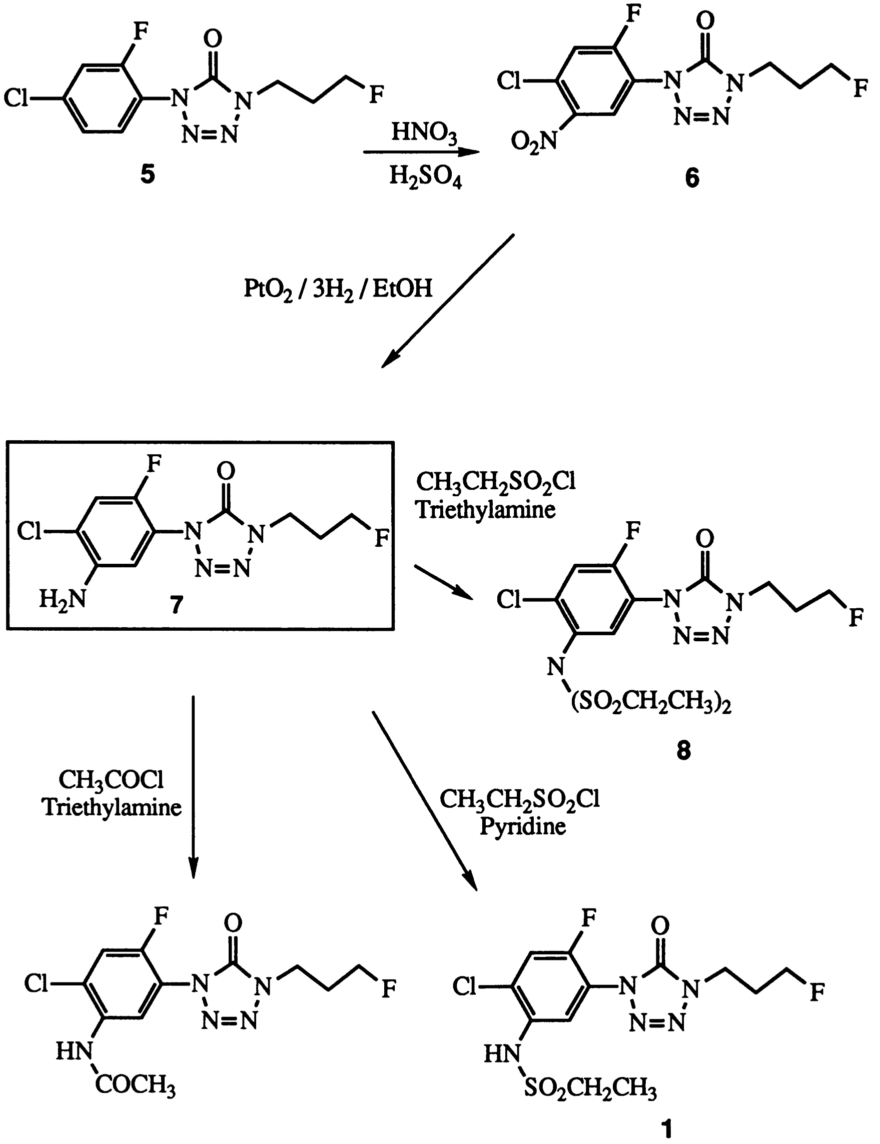

5
HNO3
H2SO4
6
PtO2 / 3H2 / EtOH
7
CH3CH2SO2Cl
Triethylamine
8
CH3COCl
Triethylamine
CH3CH2SO2Cl
Pyridine
1

Figure 7. Synthesis of analogs with nitrogen at the five position of the aromatic ring.

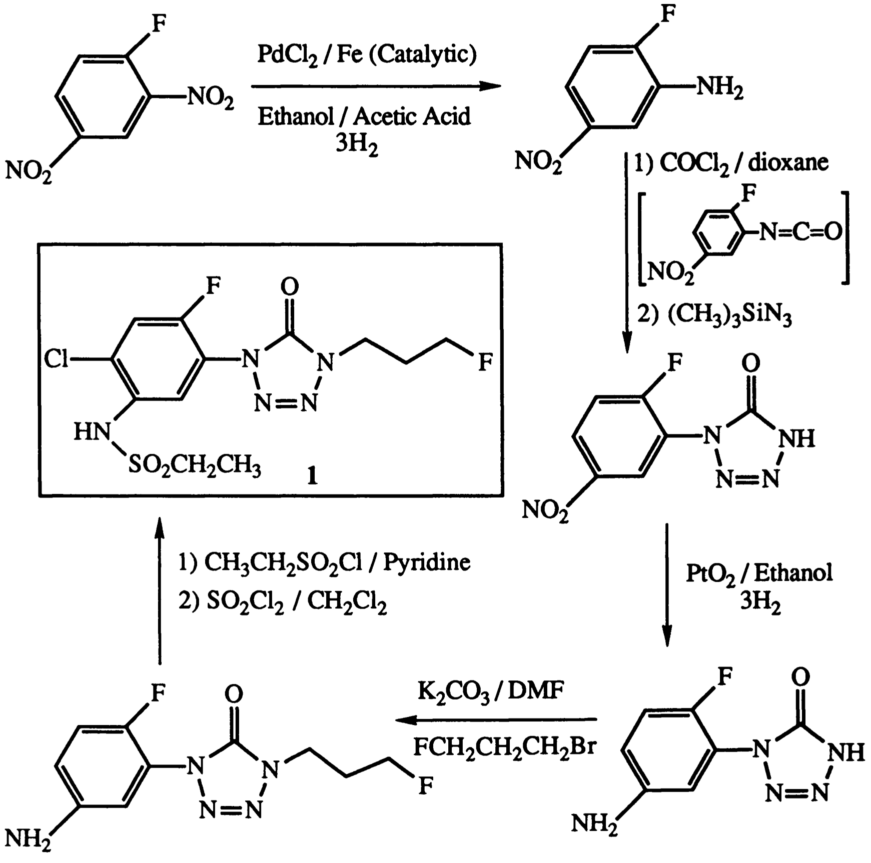
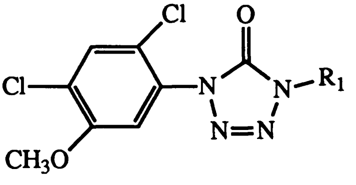

F
NO2
NO2
PdCl2 / Fe (Catalytic)
Ethanol / Acetic Acid
3H2
NH2
1) COCl2 / dioxane
N=C=O
2) (CH3)3SiN3
PtO2 / Ethanol
3H2
K2CO3 / DMF
FCH2CH2CH2Br
1) CH3CH2SO2Cl / Pyridine
2) SO2Cl2 / CH2Cl2
Cl
HN
SO2CH2CH3
O
N
NH
N=N
1

Figure 8. Alternative synthesis of compound 1.


Cl
Cl
CH3O
O
N
N
N=N
R1

Order of activity for R_1 :

$CH_2CH_2CH_2F$ > $CH_2CH{=}CH_2$ > n-C_3H_7 > C_2H_5, iso-C_3H_7 > $CH_2CH_2CH_2Cl$,

CH_2CH_2F > CH_3 >> n-C_4H_9, n-C_7H_{15}, CH_2CH_2OH, H.

Optimum activity was obtained with R_1= $CH_2CH_2CH_2F$

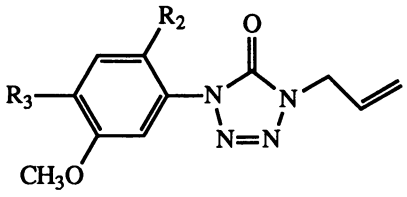
Figure 9. SAR of heterocyclic portion.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

The second large increase in activity came from the replacement with fluorine of the chlorine in the two position of the phenyl ring. It is important to note that all these improvements in biological activity were additive.

In general, the halogen groups, fluorine at position 2 (R_2), and chlorine at position 4 (R_3) of the phenyl ring provided the best activity (Figure 10).



Order of activity for R_2:

$F \gg Cl > Br > CH_3 > H > NH_2 > OCH_3$

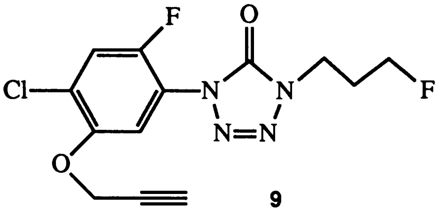
Order of activity for R_3:

$Cl > Br > CF_3, F > NO_2 > CH_3 > H > NH_2, C_6H_5$

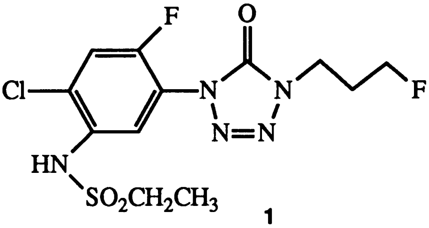
Best activity achieved when R_2 and R_3 are halogens, especially when R_2=F , R_3=Cl

Figure 10. SAR for position 2 (R_2) and 4 (R_3) of the phenyl ring.

Activity optimization of position five (R_4) resulted in the finding that a propargyloxy group, compound **9**, gave the most active compound in these series, with a broad spectrum of biological activity, controlling both grass and broadleaf weeds. Unfortunately, this compound had only marginal crop tolerance both pre- and postemergence. This high activity/low crop tolerance remained an obstacle for any practical use of these compounds as crop herbicides until the discovery that the ethanesulfonylamino group at the five position of the phenyl ring resulted in compound **1** which was not only as effective in controlling broadleaf weeds as the previous compounds but also showed excellent tolerance in several crops, such as soybean, corn, wheat, and to a lesser extent, rice.

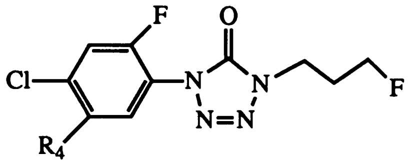


9



1

Variation in the alkyl chain of the alkylsulfonylamino group, R_4 resulted in optimum activity with ethylsulfonyl and a decrease in activity with propylsulfonyl and methylsulfonyl (Figure 11).



Order of activity for R_4 (broadleaf and grass control):

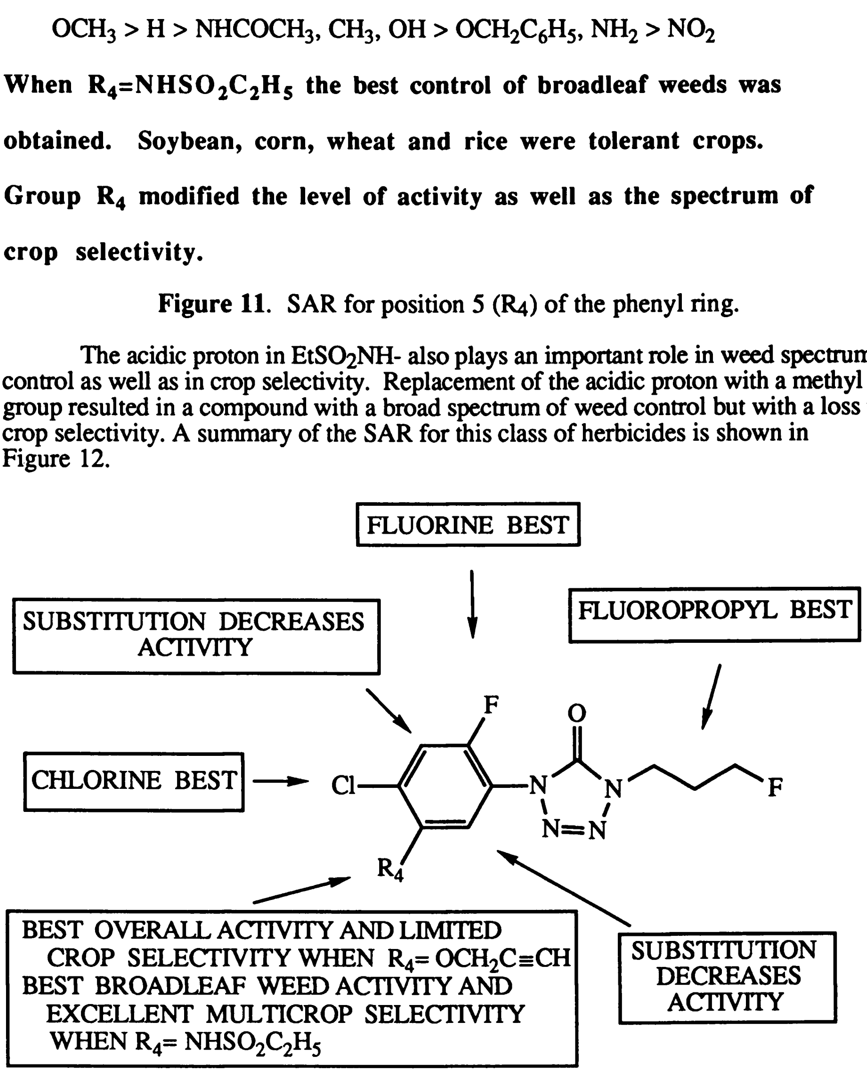
$OCH_2C{\equiv}CH > OCH(CH_3)_2 > N(CH_3)SO_2C_2H_5$, $NHSO_2(n\text{-}C_3H_7) >$

$OCH_3 > H > NHCOCH_3$, CH_3, $OH > OCH_2C_6H_5$, $NH_2 > NO_2$

When R_4=$NHSO_2C_2H_5$ the best control of broadleaf weeds was obtained. Soybean, corn, wheat and rice were tolerant crops. Group R_4 modified the level of activity as well as the spectrum of crop selectivity.

Figure 11. SAR for position 5 (R_4) of the phenyl ring.

The acidic proton in $EtSO_2NH$- also plays an important role in weed spectrum control as well as in crop selectivity. Replacement of the acidic proton with a methyl group resulted in a compound with a broad spectrum of weed control but with a loss in crop selectivity. A summary of the SAR for this class of herbicides is shown in Figure 12.


FLUORINE BEST

SUBSTITUTION DECREASES ACTIVITY

FLUOROPROPYL BEST

CHLORINE BEST

BEST OVERALL ACTIVITY AND LIMITED CROP SELECTIVITY WHEN R_4= $OCH_2C{\equiv}CH$
BEST BROADLEAF WEED ACTIVITY AND EXCELLENT MULTICROP SELECTIVITY WHEN R_4= $NHSO_2C_2H_5$

SUBSTITUTION DECREASES ACTIVITY

Figure 12. Summary of SAR of aryltetrazolinones.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

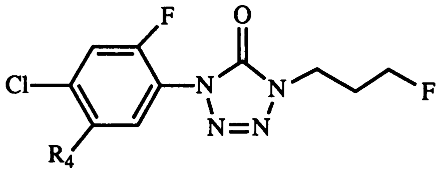
Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

Biological Activity.

All the compounds described were tested in the greenhouse pre- and postemergence on a variety of weeds and crops. The spectrum of weed control and the crop selectivity depends on the nature of the chemical group at the five position of the phenyl ring. The 5-propargyloxy derivative **9** was highly active when applied pre- or postemergence, on both grass and broadleaf weed species. Of the five crops, cotton showed the highest tolerance.

When the 5-ethylsulfonylamino derivative **1** was applied pre-emergence, excellent control of all broadleaf weeds was achieved at rates of application as low as 30 g/ha with wheat, soybean, corn and rice showing crop tolerance. No injury at all was observed with wheat and soybean. Grass weeds were not controlled. When applied postemergence, excellent broadleaf control was achieved at 15 g/ha with wheat and corn showing good tolerance (Table I).

Table I. Effect of Substituents at the Five Position of the Phenyl Ring on the Preemergence Biological Activity of Aryltetrazolinones



PHYTOTOXICITY (%CONTROL)

R_4	DOSE g a.i./ha	WHEAT	SOYBEAN	CORN	RICE	VELVETLEAF	GREEN FOXTAIL
$OCH_2C{\equiv}CH$	15	15	20	15	35	50	90
	30	50	20	50	40	90	100
	60	50	35	90	60	90	100
	125	50	60	90	90	95	100
$NHSO_2C_2H_5$	15	0	0	5	0	90	0
	30	0	0	5	5	100	0
	60	0	0	5	15	100	0
	125	0	0	15	30	100	5

Microbial Transformations of Compound 1.

The objective of this study was to identify microbial metabolites of compound **1** for subsequent use as metabolite reference standards in soil, plant, and animal metabolism studies. Details of this study have been published (*14*).

Microbial transformations of compound **1** were achieved with the filamentous fungus *Absidia pseudocylindrospora* Hasseltine et Ellis. Radiocarbon analysis showed that the majority (88-99%) of the initially added radioactivity was ethyl acetate extractable from the culture filtrates of the biotransformation cultures. HPLC analysis indicated the presence of six metabolites (Figure 13).

Both the ethylsulfonyl and fluoropropyl groups were chemically modified by the fungal enzymes. The metabolites obtained suggest that both the aromatic and tetrazolinone rings were not chemically changed.

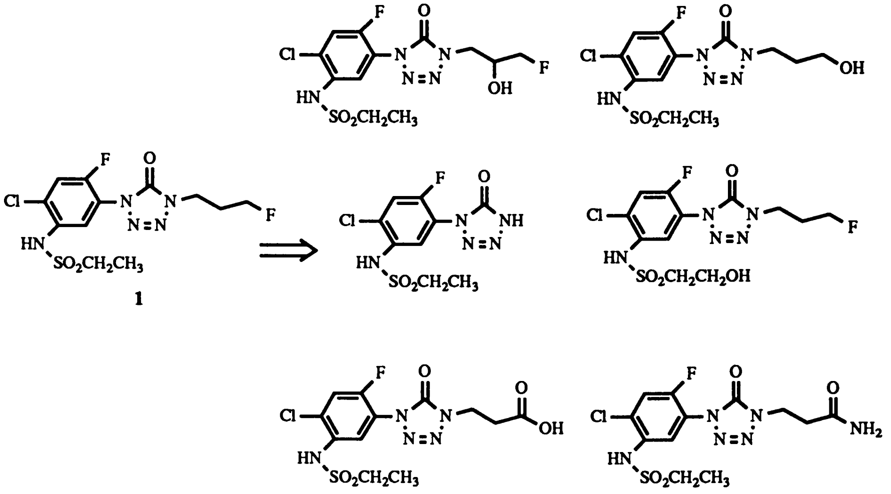


Figure 13. Compound **1** fungal metabolites.

Conclusion

1-(4-Chloro-2-fluoro-5-substituted-phenyl)-1,4-dihydro-4-(3-fluoropropyl)-5H-tetrazol-5-ones are a new and highly active family of herbicides which may be applied both pre- and postemergence. This class of chemistry demonstrates a high degree of potential for crop protection, with changes in the nature of various substituents resulting in changes in weed spectrum control and crop tolerance.

1-(4-Chloro-2-fluoro-5-ethylsulfonylamino-phenyl)-1,4-dihydro-4-(3-fluoropropyl)-5H-tetrazol-5-ones **1** represents a major breakthrough in this class of compounds, providing excellent broadleaf weed control and soybean, wheat, corn, and, to a lesser extent, rice crop tolerance. The mechanism of action involves the inhibition of protoporphyrinogen oxidase, which results in the build-up of high levels of protoporphyrin IX, a photodynamic toxicant.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

Literature Cited

1. Buchel, K.H. *Pesticide Science*, **1972**, *3*, 89.
2. Theodoridis, G. PCT Int. Patent Appln. WO 85/01939, 1985; Chem. Abstr., **1985**, *103*, 141997f.
3. Theodoridis, G. PCT Int. Patent Appln. WO 87/03873, 1987; Chem. Abstr., **1988**, *108*, 56109h.
4. Matringe, M.; Scalla, R. *Pest. Biochem. Physiol.*, **1988**, *32*, 164.
5. Witkowski, D.A.; Halling, B.P. *Plant Physiol.*, **1988**, *87*, 632. Ibid, **1989**, *90*, 1239.
6. Matringe, M.; Camadro, J.M.; Labbe, P.; Scalla, R. *Biochem. J.*, **1989**, *260*, 231.
7. Matringe, M.; Camadro, J.M.; Labbe, P.; Scalla, R. *FEBS Letters*, **1989**, *245*, 35.
8. Mito, N.; Sato, R.; Niyakado, M.; Oshio, H.; Tanaka, S. *Pest. Biochem. Physiol.*, **1991**, *40*, 128.
9. Nandihalli, U.B.; Liebl, R.A. ; Rebeiz, C.A. *Pesticide Science*, **1991**, *31*, 9.
10. Butler, R.N. *Advances in Heterocyclic Chemistry*, Academic Press, 1977, *21*, 323.
11. Benson, F.R. *Heterocyclic Compounds*, Elderfield, R.C. ed., Wiley, New York, 1967, *8*, 1.
12. Theodoridis, G.; Hotzman, F.W.; Scherer, L.W.; Smith, B.A.; Tymonko, J.M.; Wyle, M.J. *Pesticide Science*, **1990**, *30*, 259.
13. Theodoridis, G.; Manfredi, M.C.; Krebs, J.D. *Tetrahedron Letters*, **1990**, *31*, 6141, .
14. Schoken, M.J.; Theodoridis, G.; Creekmore, R.W.; Nystrom, G.J.; Robinson, R.A. *Appl. Environ. Microbiol.*, **1989**, *55*(5), 1220.

RECEIVED April 9, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch013

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Chapter 14

Synthesis and Herbicidal Properties of Aryltriazolinones

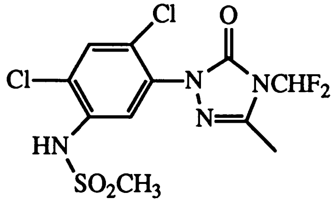
A New Class of Pre- and Postemergence Herbicides

George Theodoridis, Jonathan S. Baum, Frederick W. Hotzman, Mark C. Manfredi, Lester L. Maravetz, John W. Lyga, John M. Tymonko, Kenneth R. Wilson, Kathleen M. Poss, and Michael J. Wyle

Agricultural Chemical Group, FMC Corporation, P.O. Box 8, Princeton, NJ 08543

1-[2,4-Disubstituted-5-[N-(alkylsulfonyl) amino]phenyl-1,4-dihydro-3-methyl-4-(difluoromethyl)-5H-triazol-5-one belong to a class of highly active herbicides with a broad spectrum of weed control. They are active on both grass and broadleaf weeds at low rates. The synthesis and structure-activity relationships of these compounds will be discussed. The weed control and crop selectivity, of a specific example, F6285, will be presented in detail.

1-[2,4-Dichloro-5-[N-(methylsulfonyl) amino] phenyl-1,4-dihydro-3-methyl-4-(difluoromethyl)-5H-triazol-5-one **1** (*1,2*), F6285, is a new experimental herbicide under development by the FMC Corporation. F6285 belongs to a new class of highly active membrane disrupting herbicides, the phenyltriazolinones, and is most effective in providing broad spectrum weed control with soybean safety primarily when applied preemergence.

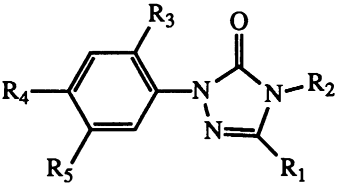


1

The mechanism of action has been found to involve inhibition of protoporphyrinogen oxidase, which results in the build-up of a photodynamic toxicant, protoporphyrin IX (*3-8*). F6285 is absorbed by plants from both the roots and shoots, with uptake from the soil occurring primarily in the apoplasm. Field trials indicate that F6285 at 0.38 lb/acre provides control of many important broadleaf weeds and selected grass species when applied either preemergence or preplant incorporated (*9*).

The synthesis, structure-activity relationship and biological activity of this new class of herbicides and related compounds of general formula 2 will be discussed.

0097–6156/92/0504–0134$06.00/0


R3
O
R4
N
N
R2
N
R5
R1

2

Synthesis

Several approaches are available for the synthesis of 1-aryl-1,2,4-triazolin-5-ones (*10-12*). We found that it was possible to prepare the heterocyclic ring in a "one pot" reaction by the condensation of the appropriate arylhydrazine with acetaldehyde to form the corresponding arylhydrazone, which is reacted, without isolation, with potassium cyanate to give the triazolidine intermediate. The oxidation of the triazolidine is accomplished by the addition of an aqueous solution of sodium hypochlorite (household bleach) or by bubbling chlorine through the solution (*13*) (Figure 1).

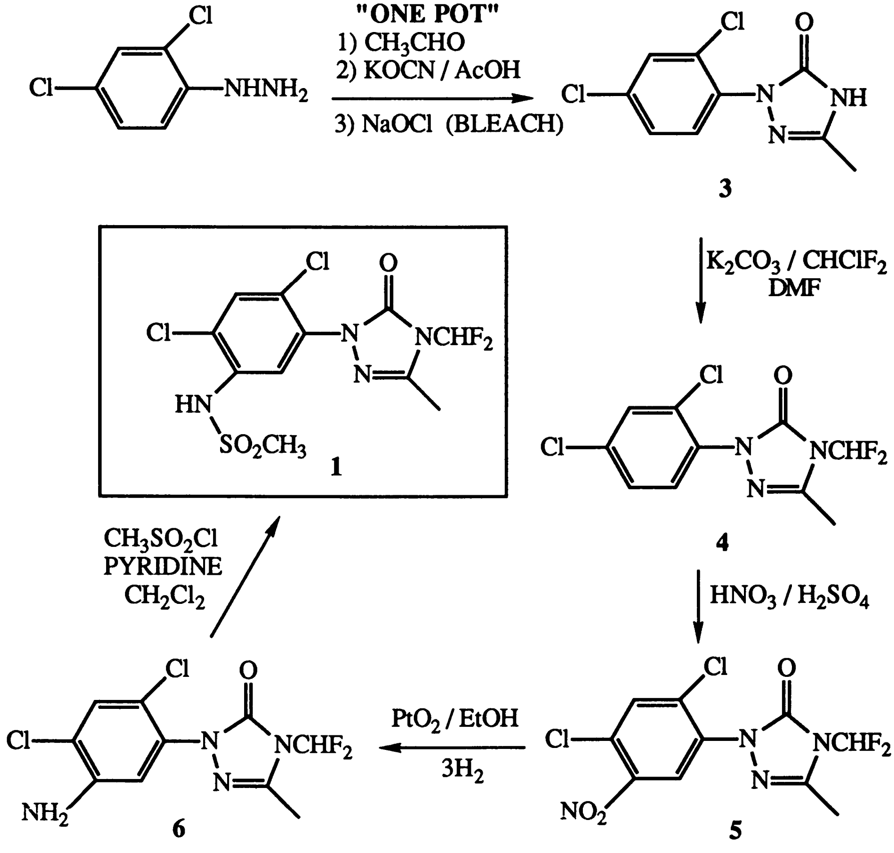

Cl
Cl
NHNH2
"ONE POT"
1) CH3CHO
2) KOCN / AcOH
3) NaOCl (BLEACH)
NH
3
K2CO3 / CHClF2
DMF
NCHF2
4
HNO3 / H2SO4
NO2
5
PtO2 / EtOH
3H2
NH2
6
CH3SO2Cl
PYRIDINE
CH2Cl2
HN
SO2CH3
1

Figure 1. General synthesis of aryltriazolinones.

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Difluoromethylation at position 4 of the triazolinone ring was accomplished by treating the 1-aryl-1,2,4-triazolin-5-one 3 with potassium carbonate and chlorodifluoromethane (Freon®-22). Under optimum reaction conditions only traces of the -OCF$_2$H isomer are obtained, which can be recycled back to starting material 3 by treatment with HCl (Figure 2).

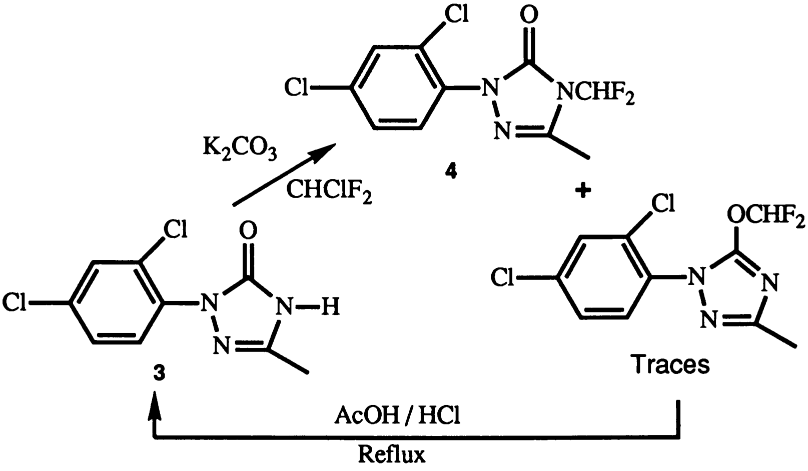

Cl
O
Cl
N
NCHF$_2$
N
K_2CO_3
$CHClF_2$
4
+
Cl
O
Cl
N
N—H
N
3
Cl
OCHF$_2$
Cl
N
N
N
Traces
AcOH / HCl
Reflux

Figure 2. Difluoromethylation of the triazolinone ring.

1-(2,4-Dichlorophenyl)-1,4-dihydro-3-methyl-4-(difluoromethyl)-5H-triazol-5-one 4 is nitrated with nitric acid in the presence of sulfuric acid, followed by catalytic hydrogenation with PtO$_2$ in ethanol to give the corresponding 1-[2,4-dichloro-5-amino]phenyl-1,4-dihydro-3-methyl-4-(difluoromethyl)-5H-triazol-5-one 6. This compound can be treated either with triethylamine and methanesulfonyl chloride to give the corresponding bis(sulfonylamino) derivative 7 or with pyridine and methanesulfonyl chloride to give F6285. Hydrolysis of the bis(sulfonylamino) derivative 7 with sodium hydroxide gives F6285 (Figure 3).

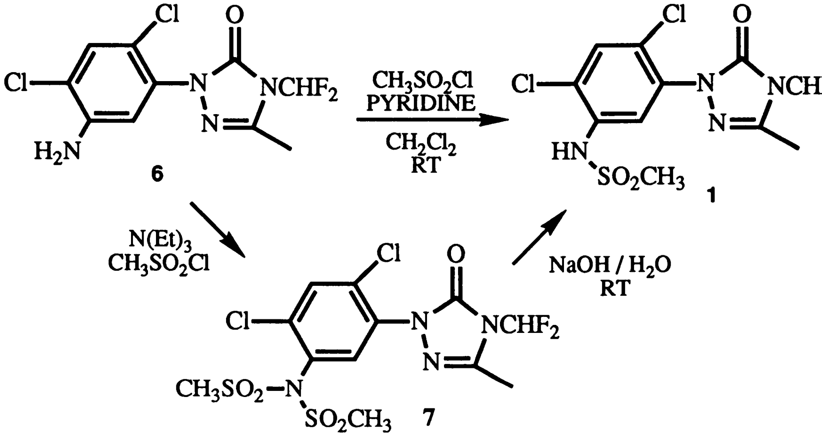

Cl
O
Cl
N
NCHF$_2$
N
H$_2$N
6
CH_3SO_2Cl
PYRIDINE
CH_2Cl_2
RT
Cl
O
Cl
N
NCHF$_2$
N
HN
SO_2CH_3
1
N(Et)$_3$
CH_3SO_2Cl
NaOH / H$_2$O
RT
Cl
O
Cl
N
NCHF$_2$
N
CH_3SO_2—N
SO_2CH_3
7

Figure 3. Mono and bis-methanesulfonylation of the amino group.

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

An alternative synthesis of the triazolinone ring involves the treatment of the appropriate phenylhydrazine with pyruvic acid to give the hydrazone **8** which is reacted with diphenyl phosphorylazide to give the desired product (*1,2,11*). This synthesis is particularly convenient in a laboratory scale (Figure 4).

Experimental details for the synthesis of compounds in Tables I-V, as well as their physical properties, have been previously published (*1,2,13-20*).

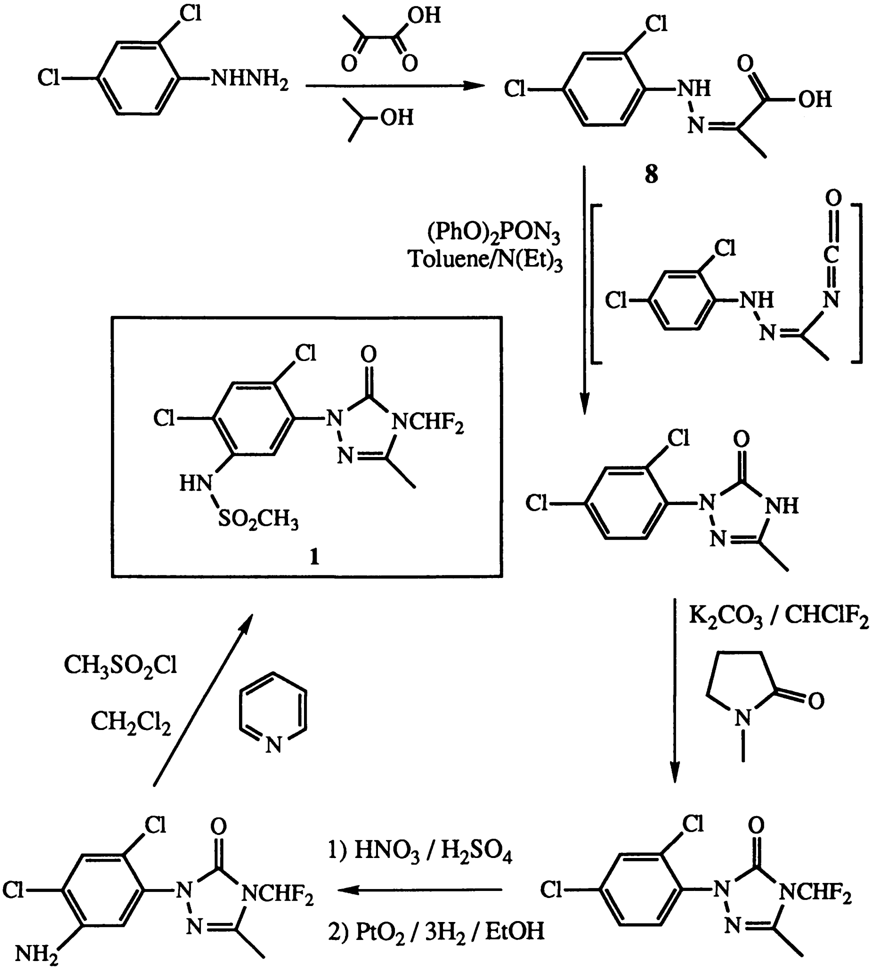

Cl
Cl
NHNH$_2$
OH
O
O
OH
Cl
Cl
NH
N
O
OH
8
(PhO)$_2$PON$_3$
Toluene/N(Et)$_3$
Cl
Cl
NH
N
O
C
N
Cl
O
Cl
N
NCHF$_2$
N
HN
SO$_2$CH$_3$
1
Cl
O
Cl
N
NH
N
K$_2$CO$_3$ / CHClF$_2$
N
O
CH$_3$SO$_2$Cl
CH$_2$Cl$_2$
N
Cl
O
Cl
N
NCHF$_2$
N
NH$_2$
1) HNO$_3$ / H$_2$SO$_4$
2) PtO$_2$ / 3H$_2$ / EtOH
Cl
O
Cl
N
NCHF$_2$
N

Figure 4. Alternative synthesis of aryltriazolinones.

Biological Testing

The compounds described were tested in the greenhouse preemergence and postemergence on various weeds and crops. The seeds of the plant test species were planted in furrows in steam-sterilized sandy loam soil contained in disposable fiber

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

flats. A topping soil of equal portions of sand and sandy loam soil was placed uniformly on top of each flat to a depth of approximately 0.5 cm.

The flats for the preemergence test were watered, then drenched or sprayed with the appropriate amount of a solution of the test compound in a mixture of acetone and water containing up to 5 ml liter $^{-1}$ of sorbitan monolaurate emulsifier/solubilizer. The concentration of the test compound in solution was varied to give a range of application rates, generally 8.0 kg ha^{-1} and submultiples thereof. The flats were placed in a greenhouse and watered regularly at the soil surface for 21 days, at which time phytotoxicity data were recorded.

Phytotoxicity data were taken as percentage control, determined by a method similar to the 0-100 rating system described previously (*21*) with 0% control of crops or weeds showing no effect relative to controls, and 100% control indicating complete crop or weed destruction. Biological data in Tables I-III are presented as the preemergence application rate required to give 90% control as compared with untreated plants. In general, the 95% confidence interval for individual ED_{90} values in these tests is $ED_{90}/2$ to $ED_{90}x2$ (e.g., the CI for an ED_{90} of 30 g ha^{-1} is 15-60). The weeds species used for Tables I-III were: morningglory, velvetleaf, johnsongrass and barnyardgrass.

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Structure-Activity Relationships

Structure activity studies were directed towards the optimization of positions 3 and 4 of the heterocyclic ring and the phenyl ring and its substituents. In general, the biological activity of this class of herbicides is highly susceptible to the nature of the chemical groups at positions 3 (R_1) and 4 (R_2) of the heterocyclic ring, as well as those at positions 2 (R_3), 4 (R_4) and 5 (R_5) of the phenyl ring.

1. Effect of Heterocyclic Ring Substituents on Biological Activity. The biological activity was highly susceptible to small changes at positions 3 (R_1) and 4 (R_2) of the triazolinone ring (Table I). In general, optimum herbicidal activity was obtained when R_1 and R_2 were small lipophilic groups.

The order of activity for R_1 is:

CH_3, CF_2H > H, CH_2CH_3 > Cl > OCH_3 , SCH_3, $CONH_2$, $CH_2C_6H_5$

The order of activity for R_2 is:

CF_2H > $CH(CH_2)_3$, CH_2CH_3, $CH_2CH{=}CH_2$ > CH_3, CH_2F

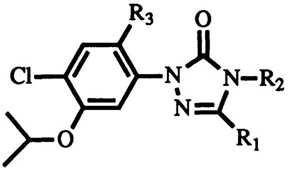
> CF_2C ClFH > $CON(CH_3)_2$, $CH_2C_6H_5$, H

2. Effect of Phenyl Ring Substituents on Biological Activity. The substituents at positions 2 (R_3) and 4 (R_4) of the phenyl ring affect herbicidal activity in a similar way to that previously published for related herbicides (*15*). As with R_1 and R_2, biological activity is highly susceptible to groups at position 2 (R_3) of the phenyl ring (Table II).

The halogens, especially fluorine, gave the highest activity. The order of activity for R_3 is:

F > Cl > H > NH_2, NO_2 , $NHSO_2CH_3$, NHCOEt

Table I. Effect of Substituents at Positions 3 and 4 of the Triazolinone Ring on the Preemergence Biological Activity of Aryltriazolinones

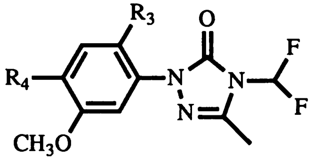


R_1	R_2	R_3	mp (°C)	Rate required to provide 90% control of weeds tested (Kg/ha)
CH_3	$CH_2CH=CH_2$	Cl	Oil	1.0
CHF_2	$CH_2CH=CH_2$	Cl	81-83	1.0
CH_2CH_3	CHF_2	Cl	83-84	2.0
H	$CH_2CH=CH_2$	Cl	83-84	>2.0
Cl	$CH_2CH=CH_2$	Cl	95-96	4.0
SCH_3	$CH_2CH=CH_2$	Cl	Oil	>8.0
OCH_3	$CH_2CH=CH_2$	Cl	Oil	8.0
$CONH_2$	$CH_2CH=CH_2$	Cl	161-162	>8.0
$CH_2C_6H_5$	CHF_2	Cl	Oil	>4.0
CH_3	CHF_2	F	77-79	0.125
CH_3	CHF_2	Cl	74-75	0.30
CH_3	$CH(CH_3)_2$	Cl	Oil	1.0
CH_3	CH_2CH_3	Cl	Oil	1.0
CH_3	CH_3	Cl	110-114	>2.0
CH_3	CH_2F	Cl	Oil	2.0
CH_3	CF_2CClFH	Cl	72-74	>4.0
CH_3	$CON(CH_3)_2$	Cl	Oil	>8.0
CH_3	$CH_2C_6H_5$	F	Oil	>8.0
CH_3	H	Cl	165-166	>8.0

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Table II. Effect of Substituents at Positions 2 and 4 of the Phenyl Ring on the Preemergence Biological Activity of Aryltriazolinones



R_3	R_4	mp (°C)	Rate required to provide 90% control of weeds tested (Kg / ha)
F	Cl	86-88	0.125
Cl	Cl	147-149	0.25
H	Cl	137-139.5	1.0
NH_2	Cl	146-149	>1.0
NO_2	Cl	175-178	>8.0
$NHSO_2CH_3$	Cl	Oil	>2.0
NHCOEt	Cl	182-184	>3.0
H	H	113-115	>8.0
F	Br	127-128	0.125
F	I	142-143	0.25
F	CF_3	117-118	0.25
F	NO_2	123-124	0.5
F	CH_3	108-110	1.0
F	CH_2CH_3	70-71	1.0
F	H	67-70	>2.0
F	NH_2	149-150	>4.0

Biological activity was less susceptible to changes at position 4 (R_4) of the phenyl ring than at either R_1, R_2 or R_3 (Table II). This biological activity was used for a quantitative structure-activity relationship (QSAR) analysis. Linear regression analysis gives the following equation:

$$\log 1/ED_{90} = 0.41\pi\ (\pm 0.09) + 1.27Fp\ (\pm 0.27) - 0.21 \qquad (1)$$

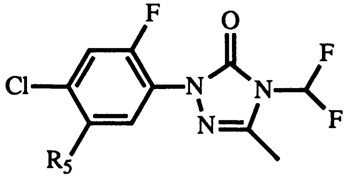
$$N=9 \qquad r^2=0.89 \qquad S=0.21 \qquad F=24$$

where π is the Hansch hydrophobicity constant and Fp is the Swain and Lupton para inductive parameter. The π and Fp term account for 89% of the variance of biological activity. For optimal activity R_4 should be a hydrophobic and electronegative group. The order of activity for R_4 is:

Cl, Br > I, CF_3 > NO_2 > CH_3, CH_2CH_3 > H > NH_2.

The substituents of positions R_1, R_2, R_3 and R_4 determine the level of herbicidal activity. The substituents at position 5 (R_5) of the phenyl ring not only influence the degree of herbicidal activity but also the weed spectrum and crop tolerance (Table III). Because of the complex relationship between R_5 groups and biological activity, weed spectrum and crop tolerance, a QSAR analysis is beyond the scope of the present work and will be addressed elsewhere.

Table III. Effect of Substituents at Position 5 of the Phenyl Ring on the Preemergence Biological Activity of Aryltriazolinones



R_5	mp (°C)	Rate required to provide 90% control of weeds tested (Kg / ha)
$OCH_2C \equiv CH$	80-81	0.030
$NHSO_2CH_3$	156-159	0.0625
$OCH(CH_3)_2$	77-79	0.0625
OCH_3	86-88	0.125
$N(CH_3)SO_2CH_3$	Oil	0.125
$NHSO_2(n\text{-}C_3H_7)$	95-96	>0.25
H	88-91	0.5
CH_3	119-120	0.5
OH	147-152	2.0
NH_2	128-129	2.0
C_6H_5	Oil	2.0
NO_2	102-104	4.0

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

The order of biological activity for R_5 (broadleaf and grass control) is:

$$OCH_2C{\equiv}CH > OCH(CH_3)_2 > OCH_3\ ,\ N(CH_3)SO_2CH_3 > NHSO_2(n\text{-}C_3H_7)$$
$$> H\ ,\ CH_3 > OH\ ,\ NH_2\ ,\ C_6H_5 > NO_2$$

When R_5=$NHSO_2CH_3$ the resulting compound gave the best control of broadleaf weeds as well as improved soybean selectivity. The soybean tolerance was further improved when R_3=R_4=Cl and R_5=$NHSO_2CH_3$, compound **1**, with little change in broadleaf control. The combination of good soybean tolerance and excellent preemergence broadleaf weed control at low application rates, as well as lower production costs when compared to the 2-fluoro (R_3=F) analogs, made F6285 a very attractive commercial candidate.

3. Effect of the Heterocyclic Ring on Biological Activity/Weed Spectrum/Crop Tolerance. So far we have investigated the effect of various substituents on the heterocycle and phenyl rings of 1-aryl-1,2,3-triazolinones. We now turn to the potential impact that different heterocyclic rings have on biological activity. Our study will be limited to the preemergence activity of five heterocyclic rings.

As can be seen from Table IV, when R_5=$OCH_2C{\equiv}CH$, the level of biological activity varies greatly with the heterocyclic ring, the triazolin-5-one ring gives the highest level of biological activity. All five examples provided better control of grass weeds than broadleaf weeds with no clear crop tolerance for either wheat, soybean or corn.

Completely different results were obtained when R_5=$NHSO_2CH_3$: not only did we observe a variation of the level of biological activity with different heterocycles, but this time the spectrum of weed control and crop tolerance greatly varied with each different heterocycle (Table V).

This time better broadleaf weed control than grass control is obtained with all heterocycles. The most striking result is the excellent wheat, soybean and corn crop tolerance observed for the tetrazolinone ring (*15*), and the soybean tolerance obtained with the triazolinone ring when X=Cl, both at low rates of application. There is also a dramatic change in spectrum of weed control when going from the tetrazolinone ring, a broadleaf weed herbicide, to the triazolinone ring, a grass and broadleaf herbicide. In general (this applies to preemergence application only):

When R_5=$OCH_2C{\equiv}CH$ the heterocyclic ring will:

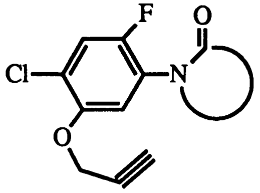
1) Influence the degree of biological activity
2) Give better grass than broadleaf weed control
3) Has small impact on crop selectivity

When R_5=$NHSO_2CH_3$ the heterocyclic ring will:

1) Influence the degree of biological activity
2) Give better broadleaf than grass weed control
3) Influence the degree of either grass or broadleaf control
4) Affect the degree of crop tolerance.

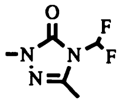
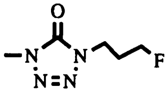
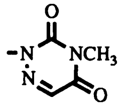
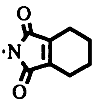
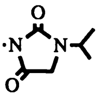
Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Table IV. Effect of the Heterocyclic Ring on the Preemergence Biological Activity of 2-Fluoro-4-chloro-5-propargyloxy Derivatives



GREENHOUSE PREEMERGENCE ACTIVITY

PHYTOTOXICITY (% CONTROL)

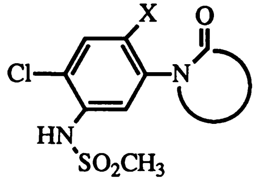
HETEROCYCLIC RING	DOSE grams a.i./ha	WHEAT	SOYBEAN	CORN	MORNING GLORY	GREEN FOXTAIL
	15	50	80	95	80	100
	62.5	50	35	90	70	100
	62.5	50	20	70	60	100
	125	50	30	40	80	90
	125	100	60	100	90	100

Herbicidal Activity

The preemergence herbicide activity of compound **1**, F6285, is shown in Table VI. These data were obtained from greenhouse tests in preemergence applications on a variety of weeds and crops. These weeds were morningglory, velvetleaf, nutsedge, green foxtail and barnyardgrass. F6285 demostrates excellent control of a number of broadleaf weeds while providing weed control of a number of grass species and nutsedges, with good safety on soybeans. Field trials indicate that F6285 at 0.38 lb/acre provides control of many important broadleaf weeds and selected grass species when applied either preemergence or preplant incorporated.

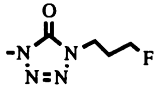
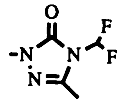
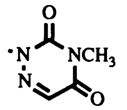
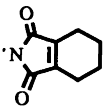
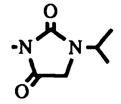
Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Table V. Effect of the Heterocyclic Ring on the Preemergence Biological Activity of 2-Fluoro-4-chloro-5-methylsulfonylaminophenyl Derivatives



GREENHOUSE PREEMERGENCE ACTIVITY

PHYTOTOXICITY (% CONTROL)

HETEROCYCLIC RING	X	DOSE gr a.i./ha	WHEAT	SOYBEAN	CORN	MORNING GLORY	GREEN FOXTAIL
	F	**62.5**	0	0	0	90	0
	F	**62.5**	40	20	60	100	80
	Cl		5	0	5	100	85
	F	**62.5**	10	50	30	95	80
	F	**250**	5	0	30	100	15
	F	**500**	10	20	40	95	50

Summary

In summary, F6285 is a new and effective soybean herbicide with a wide spectrum of activity on many broadleaf and grass weeds. F6285 is particularly effective against morningglory and nutsedge weeds. F6285 will also provide excellent control of common cocklebur in the southern United States, when applied either preemergence or preplant incorporated. No rotational crop restrictions are expected for corn, small grains, sorghum, rice, peanut, sunflower or legumes. Cotton and sugarbeet are sensitive, and may require rotation restrictions. (See Figure 5.)

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

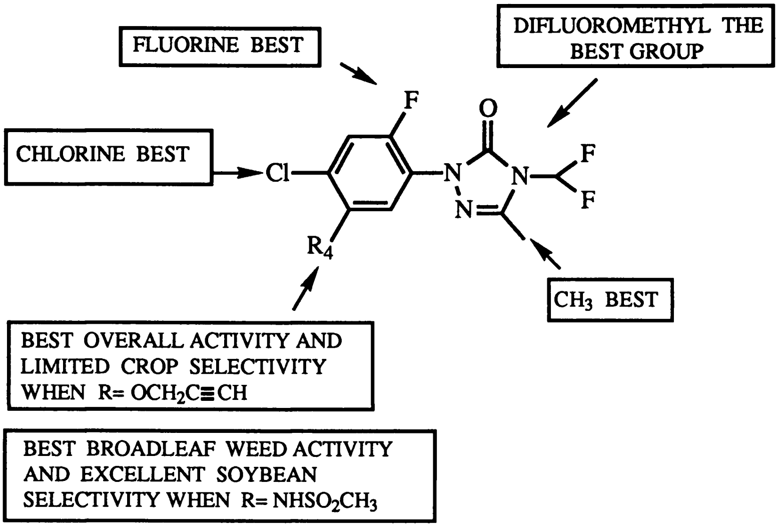
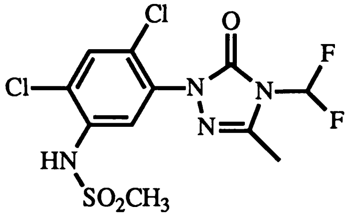

FLUORINE BEST
DIFLUOROMETHYL THE BEST GROUP
CHLORINE BEST
F
O
Cl
N
N
N
F
F
R4
CH3 BEST
BEST OVERALL ACTIVITY AND LIMITED CROP SELECTIVITY WHEN R= OCH2C≡CH
BEST BROADLEAF WEED ACTIVITY AND EXCELLENT SOYBEAN SELECTIVITY WHEN R= NHSO2CH3

Figure 5. Summary of SAR of aryltriazolinones.

Table VI. Preemergence Activity of 1-[2,4-Dichloro-5-[N-(methylsulfonyl)amino]phenyl-1,4-dihydro-3-methyl-4-(difluoromethyl)-5H-triazol-5-one


Cl
O
Cl
N
N
N
F
F
HN
SO2CH3

	PHYTOTOXICITY (% CONTROL) [a]							
Dose (g/ha)	Wheat	Soybean	Corn	Morning-glory	Velvetleaf	Nutsedge	Green foxtail	Barnyard-grass
31.3	0	0	0	85	100	60	30	15
62.5	5	0	5	100	100	85	85	60
125.0	15	10	20	100	100	95	90	95
250.0	40	10	70	100	100	100	100	100

[a] Average of four greenhouse tests.

Acknowledgements

The authors would like to acknowledge the contributions of Blaik P. Halling, Debra A. Witkowski and M. Joan Plummer, for their work in elucidating the mechanism of action of these herbicides (*4*). We also would like to express our thanks to James T. Bahr, Guy A. Crosby and William A. Van Saun for their encouragement and advice.

Literature Cited

1. Theodoridis, G. U.S. Patent 4,818,275, 1989.
2. Theodoridis, G. U.S. Patent 5,041,155, 1991.
3. Matringe, M.; Scalla, R. *Pest. Biochem. Physiol.* **1988**, *32*, 164
4. Witkowski, D.A.; Halling, B.P. *Plant Physiol.* **1988**, *87*, 632. Ibid, **1989**, *90*, 1239.
5. Matringe, M.; Camadro, J-M.; Labbe, P.; Scalla, R. *Biochem J.* **1989**, *260*, 231.
6. Matringe, M.; Camadro, J-M.; Labbe, P.; Scalla, R. *FEBS Letters* **1989**, *245*, 35.
7. Mito, N.; Sato, R.; Miyakado, M.; Oshio, H.; Tanaka, S. *Pest. Biochem. Physiol.* **1991**, *40*, 128.
8. Nandihalli, U.B.; Liebl, C.A. *Pesticide Science.* **1991**, *31*, 9.
9. Van Saun, W.A.; Bahr, J.T.; Crosby, G.A.; Fore, Z.A.; Guscar, H.L.; Harnish, W.N.; Hooten, R.S.; Marquez, M.S.; Parrish, D.S.; Theodoridis, G.; Tymonko, J.M.; Wilson, K.R.; Wyle, M.J. *Proc. Br. Crop Protection Conf., Weeds,* **1991**, *1*, 77
10. Temple Jr. C. *Triazoles 1,2,4; The Chemistry of Heterocyclic Compounds,* Volume 37, A. Weissberger and E.C. Taylor; eds. John Wiley and Sons, New York, NY, 1981, p. 365-403.
11. Lyga, J.W. *Synth. Comm.* **1986**, 163.
12. Ray, P.S.; Hank, R.F. *J. Heterocyclic Chem.* **1990**, *27*, 2017.
13. Theodoridis, G.; Lyga, J.W. U.S. Patent 4,980,480, 1988.
14. Kajioka, M.; Okawa, K.; Taninaka, K.; Kurono, H.; Harada, T. U.K. Patent Application 2,056,971, 1981.
15. Theodoridis, G.; Hotzman, F.W.; Scherer, L.W.; Smith, B.A.; Tymonko, J.M.; Wyle, M.J. *Pesticide Science* **1990**, *30*, 259.
16. Kajioka, M.; Okawak.; Taninaka, K. U.K. Patent Application 2,090,250, 1982.
17. Theodoridis, G.; Maravetz, L.L. U.S. Patent 4,818,276, 1989.
18. Lyga, J.W.; U.S. Patent 4,766,233, 1988.
19. Nagano, E.; Hashimoto, S.; Yoshida, R.; Matsumoto, H.; Kamoshita, K. European Patent Application 69,855, 1983.
20. Nagano, E.; Hashimoto, S.; Yoshida, R.; Matsumoto, It.; Kamoshita, K. U.S. Patent 4,484,941, 1984.
21. Frans, R.E. & Talbert, R.E.; *In Research Methods in Weed Science,* 2nd edn, ed. B. Truelove, Auburn, AL, 1977, pp 15-23.

RECEIVED April 27, 1992

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch014

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

Chapter 15

Novel Pyrazole Phenyl Ether Herbicides

Kurt Moedritzer, Sarah G. Allgood, Pana Charumilind, Robert D. Clark, Bruce J. Gaede, Mitchell L. Kurtzweil, Deborah A. Mischke, John J. Parlow, Michael D. Rogers, Rajendra K. Singh, Gina L. Stikes, and R. Keith Webber

Monsanto Agricultural Company, St. Louis, MO 63167

From a recently discovered new pyrazole derivative and its known regioisomer, two classes of novel, regioisomeric pyrazole phenyl ethers (phenoxypyrazoles) were synthesized. Structure/activity studies of sets of the two isomeric phenoxypyrazoles showed that 3-phenoxypyrazoles, generally, are orders of magnitude more active as herbicides than are the corresponding 5-phenoxypyrazoles. Within the class of 3-phenoxypyrazoles the nature of the substituents on the pyrazole and phenyl moieties determined herbicide activity, crop selectivity, weed spectrum and field performance.

In the course of exploring certain synthetic aspects of pyrazole chemistry, a trisubstituted pyrazole was prepared which, as a key feature, contained a trifluoromethyl group attached to one of the ring carbon atoms. This pyrazole, in greenhouse evaluations, showed moderate herbicide activity. In reviewing the literature on such trifluoromethyl substituted pyrazoles, in particular pyrazoles which, in addition to the trifluoromethyl group, were ring substituted with functional groups suitable for further derivatization, a paper by DeStevens and coworkers *(1)* was found. This paper describes the reaction of ethyl 4,4,4-trifluoroacetoacetate (ETFAA) with methylhydrazine to give 1-methyl-3-trifluoromethyl-5-hydroxypyrazole in about 25% yield (Figure 1). No mention was made in this paper, however, of the corresponding isomeric 3-hydroxypyrazole shown in Figure 1, which could also be a potential reaction product.

Each of these isomers, of course, is assumed to be in a tautomeric equilibrium with its corresponding pyrazolone(s), that is, where the hydroxyl group is tautomerized to a carbonyl. An additional feature of this particular pyrazole was that the oxy substituent (hydroxyl group or tautomeric carbonyl group), on the pyrazole could now provide a suitable functional group for further elaboration and allow the preparation of a diverse range of derivatives.

American Chemical Society
Library
1155 16th St., N.W.
Washington, D.C. 20036

0097-6156/92/0504-0147$06.00/0

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

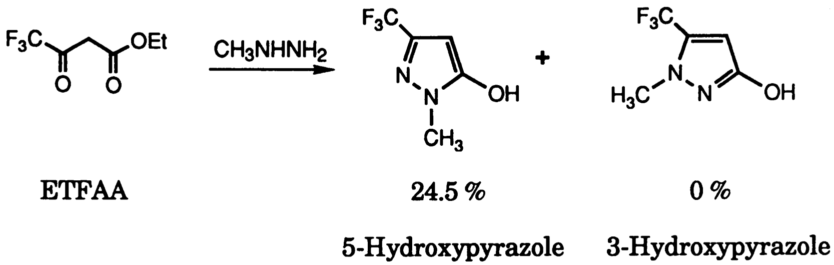

ETFAA
CH3NHNH2
24.5 %
0 %
5-Hydroxypyrazole
3-Hydroxypyrazole

Figure 1.

Regioselective Syntheses of Pyrazole Precursors

When the DeStevens reaction was repeated in our laboratories *(2,3)*, the 3-hydroxy regioisomer was detected and identified in the reaction product, in addition to the reported 5-hydroxypyrazole. The ratio of the two regioisomers in the product was about 1:4 (Figure 2). Separation of the two regioisomers was very facile since the 5-hydroxy isomer was soluble in aqueous $NaHCO_3$ solution and the 3-hydroxy isomer was not.

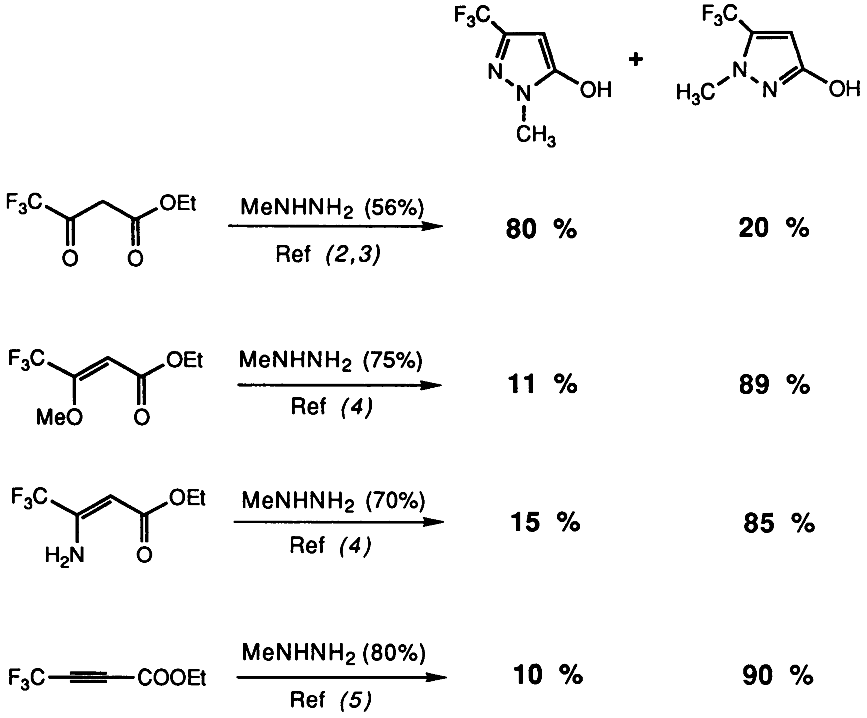

MeNHNH2 (56%)
Ref (2,3)
80 %
20 %
MeNHNH2 (75%)
Ref (4)
11 %
89 %
MeNHNH2 (70%)
Ref (4)
15 %
85 %
MeNHNH2 (80%)
Ref (5)
10 %
90 %

Figure 2.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

The 3-hydroxy isomer was of particular interest, because it had not been reported in the literature and thus could serve as synthon for novel and proprietary chemistry. This compound and related compounds are disclosed in a composition of matter U. S. Patent *(3)* issued to Monsanto Company.

Unfortunately, the DeStevens reaction was not very efficient in producing the desired 3-hydroxypyrazole regioisomer. With the goal of improving the yield of this regioisomer, new methods were developed *(4,5)* at Monsanto which dramatically reversed the regiochemistry in favor of the 3-hydroxypyrazole. Using these methods, the pyrazole forming reaction could now be run so that the 3-hydroxy isomer was the major product and the 5-hydroxy isomer was the minor one. The equations depicting these methods are given in Figure 2.

All of the methods shown above worked quite well and proceeded in excellent yields. The enol ether starting material in the second equation above was obtained from ETFAA and dimethyl sulfate; the enamine starting material in the third equation was obtained from ETFAA and anhydrous ammonia; and ethyl 4,4,4-trifluoro-2-butynoate was obtained by an improved literature procedure *(6,7)*.

Pyrazole Phenyl Ethers (Phenoxypyrazoles)

Having high-yield, reliable syntheses of both regioisomers of trifluoromethyl substituted hydroxypyrazoles in hand, corresponding phenyl ethers were prepared, specifically, ethers where the substituent pattern on the phenyl group resembled that of the well known diphenyl ether (DPE) herbicides *(8)*. Depending on the regioisomer of the pyrazole used as starting material, 3-phenoxypyrazoles or 5-phenoxypyrazoles were obtained (Figure 3). The ether forming reactions worked quite well when either of the hydroxypyrazole isomers was reacted with a *para*-nitro activated fluorobenzene to give the corresponding ether. Reaction conditions were DMSO as solvent, 70° overnight and K_2CO_3 as base. The 4-position on the pyrazole of the pyrazole phenyl ethers could then be chlorinated, or the hydroxypyrazole could be chlorinated first, resulting in a 4-chloropyrazole, which could be coupled to form the corresponding ether. The chlorinating agent "Cl" was either Cl_2, SO_2Cl_2 or 1,3-dichloro-5-5-dimethylhydantoin.

The compounds prepared by this scheme were pyrazole phenyl ethers (PPEs) and as such were structurally related to the diphenyl ether herbicides, with one of the phenyl groups in DPEs replaced by a very specific pyrazole. Some classes of these novel pyrazole phenyl ethers indeed showed significant herbicide activity. It turned out that only one of the regioisomeric phenoxypyrazoles, the 3-phenoxypyrazoles, showed useful herbicide activity on whole plants in the greenhouse. The analogous 5-phenoxypyrazoles were much less active or sometimes totally inactive at application rates up to 10 lb/acre.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

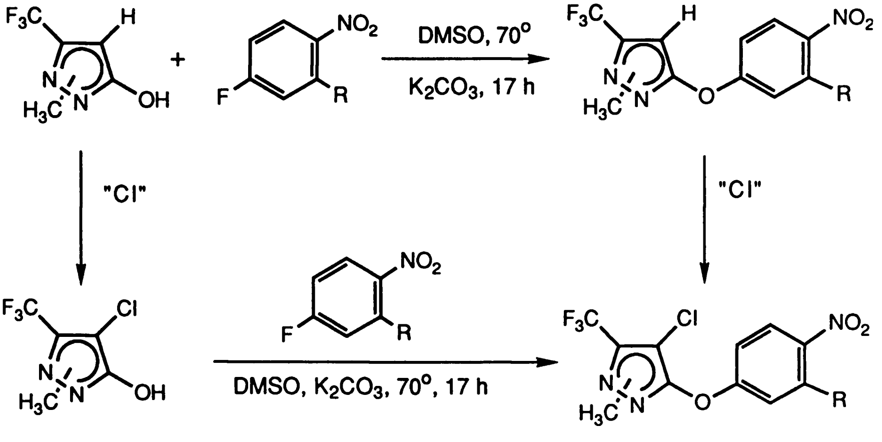
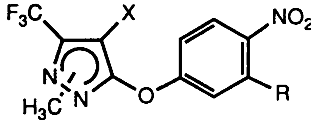


Figure 3.

Germination Assays. A semi-quantitative evaluation of the differences in biological activity for the two isomeric phenoxypyrazoles was obtained from a germination assay *(9)* of barnyardgrass seedlings as shown in Table 1.

Table I. Germination Assays (Barnyardgrass) of Pairs of Regioisomers of Phenoxypyrazoles



		I_{50} (μM)	
X	R	3-Phenoxy	5-Phenoxy
H	H	36	>1000
Cl	H	8	160
H	Me	74	>1000
H	COOH	5	>1000
H	COOEt	7	>1000
Cl	COOEt	2	170
Cl	COOMe	1	280
H	COOCHMeCOOEt	210	730
Cl	COOCHMeCOOPr	2	>1000
H	OEt	15	>1000
Cl	OEt	2	380

The results of this study are expressed in terms of I_{50} values, which are the μM concentrations of compound which cause a 50% reduction in root growth of barnyard grass seedlings relative to control. The smaller the I_{50}, the greater the growth inhibiting activity. The data showed that, *e.g.*, for X = R = H, the 3-phenoxy isomer was at least 30x more active than the corresponding 5-phenoxy isomer. A similar trend was seen for the other isomer pairs in this table.

These studies showed further that for pairs of compounds where R was identical, replacing a hydrogen by a chlorine at the 4-position ("X") of the pyrazole moiety increased the biological activity significantly. This was true for both isomers and has been confirmed in greenhouse studies on whole plants.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

Molecular Modeling. One of the four minimum energy state conformations (Sybyl 3.0, Tripos Associates, St. Louis, MO) is shown for each isomer in Figure 4 to illustrate the differences in the spatial arrangement. On the left in Figure 4 is the 3-phenoxypyrazole, which is the active regioisomer, and on the right is the 5-phenoxypyrazole, which is the inactive one. From these drawings it is easily seen that the general spatial arrangement of atoms of both compounds is very similar, such as the bond angle around the bridging oxygen, the angle between the planes of the two rings, and the positions of the trifluoromethyl group and the chlorine atom on the pyrazole moiety. The only difference is the position of the methyl group attached to the nitrogen atom in the pyrazole moieties. This is specifically illustrated in Figure 5 which represents an overlap of the two regioisomeric pyrazole phenyl ethers in Figure 4 with the space occupied by the two methyl groups highlighted.

Mode of Action of Pyrazole Phenyl Ethers. In recently published *in vitro* experiments *(10)* of the effects of several pyrazole phenyl ethers (both regioisomers) on cucumber cotyledon and barley primary leaf tissue sections, it was found that these compounds were protoporphyrinogen IX oxidase (Protox) inhibitors. The observed greater phytotoxicity of 3-phenoxypyrazoles relative to corresponding 5-phenoxypyrazoles correlated well with their capacity to inhibit Protox *in vitro*. Other known Protox inhibitors are the DPEs, oxadiazoles, N-phenylimides and other polycyclic compounds. Similar to other such inhibitors, pyrazole phenyl ethers caused rapid accumulation of protoporphyrin IX (PPIX) by inhibiting protophorphyrinogen IX oxidase, which is the last common enzyme to the synthesis of both heme and chlorophylls. The accumulated protoporphyrin IX is a photosensitizer which mediates light-dependent cellular membrane destruction.

Single Crystal X-Ray Structure Determination. The modeling studies were consistent with a single crystal X-ray structure determination of a typical 3-phenoxypyrazole shown in Figure 6. The C_3-O-C_6 bond angle in the above pyrazole phenyl ether is 119° and the two rings are not in the same plane, the dihedral angle between the least-square mean planes of the pyrazole ring and phenyl ring is 105°.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

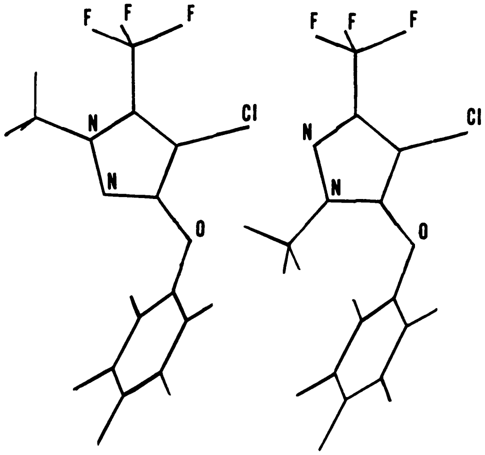


Figure 4. Computer Modeled Energy-Minimized Conformations of 3-Phenoxypyrazole (left) and 5-Phenoxypyrazole (right)

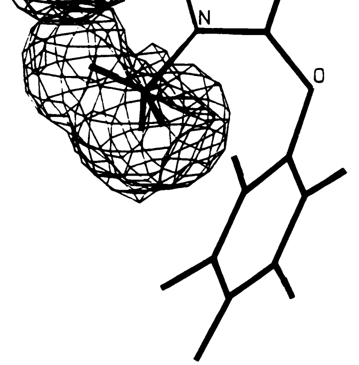


Figure 5. Overlap of 3- and 5-Phenoxypyrazoles with the Space of the Methyl Groups Highlighted

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

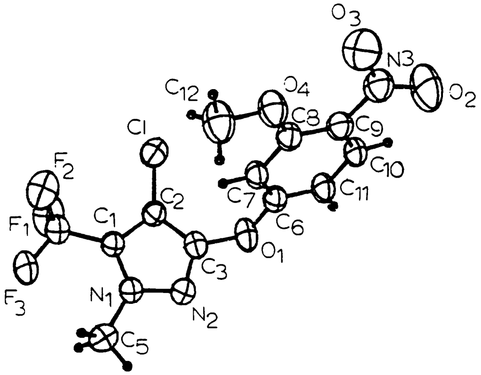
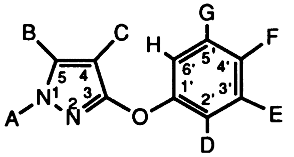

O3
N3
O2
C12
O4
C8
C9
Cl
F2
C10
C7
C11
C2
C1
C6
F1
O1
C3
F3
N1
N2
C5

Figure 6. Structure of 4-Chloro-3-(3-methoxy-4-nitrophenoxy)-1-methyl-5-(trifluoromethyl)-1H-pyrazole as Determined by a Single Crystal X-ray Study

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

Herbicide Activity. Many derivatives of 3-phenoxypyrazole were prepared and were found to be very active as herbicides in the greenhouse as well as in the field showing high unit activity, in many instances good crop selectivity, and a good weed spectrum. For certain compounds we have seen better than 80% control of specific weeds at rates lower than 0.01 lb/acre. However, in this paper the emphasis will be on a discussion of some of the chemistry that was employed to explore the structure/activity relationships of the various sites in the general 3-phenoxypyrazole structure below and not on the details of biological activity.

Theoretically, there are 8 sites bearing substituents in the pyrazole phenyl ether molecule - 3 on the pyrazole and 5 on the phenyl group - which can have an effect on the over-all herbicide activity, crop selectivity, weed spectrum, field performance and physical properties of these compounds.

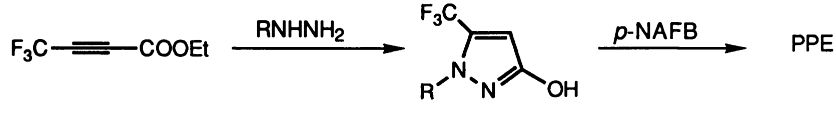


Exploring the structure/activity relationship of these 8 sites could have easily turned into a monumental task. If one considers just 3 different substituents for each of the 8 sites, permutation and combination results in 8^3 different species or 512 compounds, a manageable number. When one considers 10 different substituents, this number is 8^{10}, more than a billion compounds. Of course, a much smaller number of compounds actually were prepared. Our issued U. S. Patent *(11)* includes over 900 synthesized and tested examples.

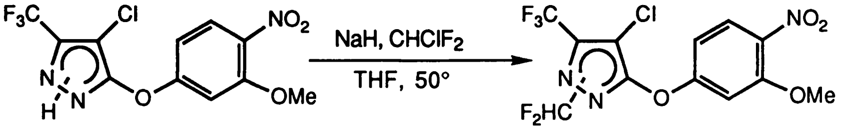
Variation of Substituents in Pyrazole Phenyl Ethers

In the following, details will be discussed of reactions that were employed to vary some of the key substituents on the various sites of the parent 3-phenoxypyrazole structure.

Variation of Pyrazole 1-Position. 3-Hydroxypyrazoles with different substituents at the 1-position of the pyrazole moiety, that is the substituent on the pyrazole nitrogen, were prepared by simply using, instead of methylhydrazine, other alkyl hydrazines, $RNHNH_2$, to form the pyrazole precursors. This worked quite well for R = Et, *n*-Pr, *i*-Pr, *n*-Bu, CH_2CH_2OH or benzyl and the resulting 3-hydroxypyrazoles coupled readily with *para*-nitro activated fluorobenzenes (*p*-NAFB) to give the corresponding PPEs in good yields. However, for R = CH_2CF_3 or *t*-Bu the other regioisomeric pyrazole, the 5-hydroxypyrazole, was the only product that formed.

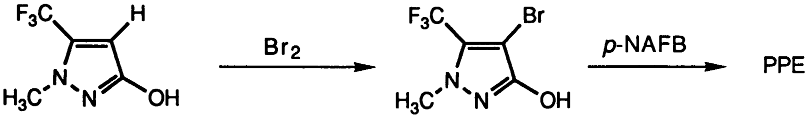


Another approach had to be taken to place CF_2H as substituent at the pyrazole nitrogen. Here the 1-hydrogen derivative of the PPE was prepared first, from the 1-H hydroxypyrazole *via* a multi-step reaction sequence involving NH protection, ether coupling and deprotection to restore the NH function, and the resulting PPE was then difluoromethylated with CHF_2Cl in strong base to give a 1:1 mixture of the regioisomers of the corresponding pyrazole phenyl ethers. These were separated by radial chromatography.

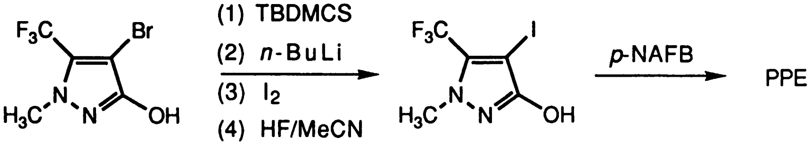


The corresponding 1-CF_3 substituted PPE compound was prepared similarly, using CF_2Br_2 to give the two regioisomers of the 1-CF_2Br substituted PPEs, separation of the two regioisomers, and displacement of Br in the 1-CF_2Br group by F with silver fluoroborate.

Variation of Pyrazole 4-Position. The hydrogen at the 4-position, on the pyrazole itself as well as the pyrazole moiety in PPEs, was easily chlorinated as shown earlier. Bromination occurred equally well at this position using Br_2 or 1,3-dibromo-5,5-dimethylhydantoin, and in the case of the hydroxypyrazole itself, subsequent ether coupling with *para*-nitro activated fluorobenzenes (*p*-NAFB) gave the corresponding PPEs.



However, attempts to prepare the corresponding 4-iodopyrazole by simply treating the 4-H pyrazole with I_2 were not successful. Iodine was be incorporated at this position by lithiation chemistry, starting from the 4-bromopyrazole *via* the following steps: (1) OH protection with *t*-butyldimethylchlorosilane (TBDMCS), (2) lithiation with *n*-BuLi, (3) reaction with elemental iodine, (4) deprotection of the OH group with aqueous HF/acetonitrile and (5) coupling with *para*-nitro activated fluorobenzene (*p*-NAFB) to form the desired PPE.



Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

Special procedures also had to be worked out for the incorporation of fluorine at the 4-position in the pyrazole (Figure 7). Claisen condensation of ethyl trifluoroacetate with ethyl fluoroacetate gave the ethyl 2,4,4,4-tetrafluoroacetoacetate *(12)*. This was converted to the enol ether with dimethylsulfate and the enol ether was reacted with methylhydrazine. From the mixture of products thus obtained, the desired pyrazole isomer was separated in 40% regioselective yield and coupled with a *para*-nitro activated fluorobenzene to give the PPE.

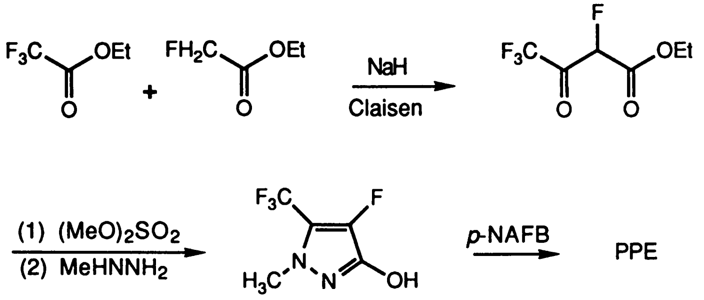


Figure 7.

Although the pyrazole could be easily nitrated at the 4-position, the resulting nitropyrazole was chemically quite inert and did not react readily with most *para*-nitro activated fluorobenzenes (*p*-NAFB) because the nucleophilicity of the hydroxy group in the nitro pyrazole was significantly reduced by the neighboring nitro group. However, by simply reversing the order of the two reactions, the desired 4-nitro PPE could be obtained readily for some phenyl substitution patterns (Figure 8). The 4-H pyrazole was first coupled to form the PPE and then the pyrazole moiety of the PPE was easily and selectively nitrated at the 4-position of the pyrazole to give the desired 4-nitro PPE.

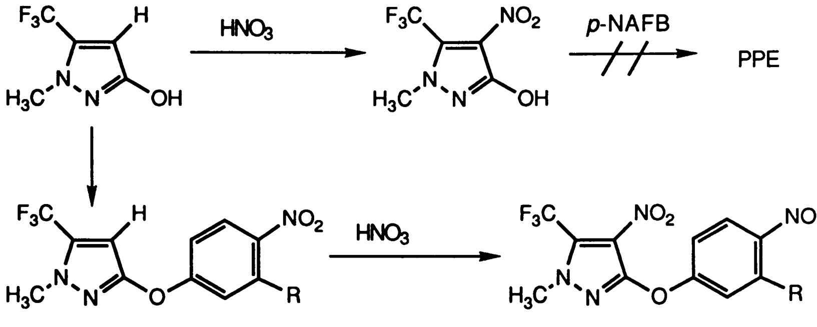


Figure 8.

Variation of Pyrazole 5-Position. Incorporation of $S(O)_nR$ (n = 0, 1 or 2, R = Me, Et) at the 5-position on the pyrazole moiety, was based on a patent

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

reference *(13)*. According to the latter, one of the chlorines on carbon atom 3 in methyl trichloroacrylate could be displaced by an alkylthio group *e.g.*, a methylthio group (Figure 9). The resulting methylthio acrylate, upon reaction with methylhydrazine, gave exclusively the desired pyrazole regioisomer. The regiochemistry of this pyrazole was confirmed by a single crystal X-ray analysis. This pyrazole reacted smoothly with *para*-nitro activated fluorobenzenes to give the expected PPEs and the latter could be oxidized to the corresponding sulfoxides or sulfones.

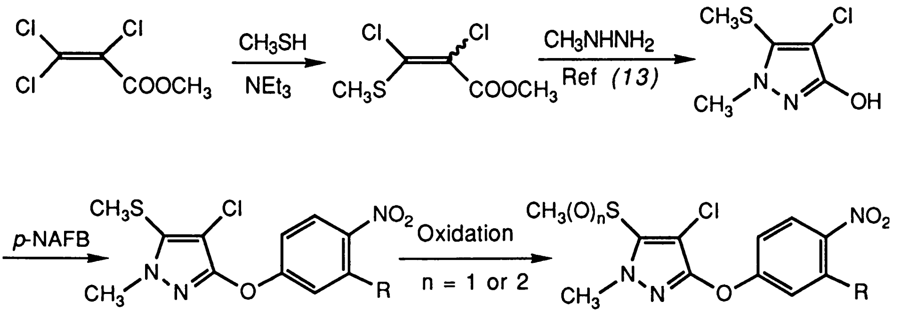

Cl
Cl
Cl
COOCH3
CH3SH
NEt3
Cl
Cl
CH3S
COOCH3
CH3NHNH2
Ref (13)
CH3S
Cl
CH3
N
N
OH
p-NAFB
CH3S
Cl
CH3
N
N
O
NO2
R
Oxidation
n = 1 or 2
CH3(O)nS
Cl
CH3
N
N
O
NO2
R

Figure 9.

Several other groups at the 5-position were incorporated via lithiation chemistry and electrophilic substitution. A general approach is shown below. The starting pyrazole carboxylate ester, available from dialkyl acetylenedicarboxylate and methylhydrazine *(14)*, was chlorinated at the 4-position, the carboxylate ester hydrolyzed and the acid decarboxylated to the corresponding 4-chloropyrazole, the OH group protected with *t*-butyldimethylchlorosilane, the 5-position lithiated, substituted with an electrophile and deprotected. This sequence produced the desired hydroxypyrazole for coupling to form the PPE (Figure 10).

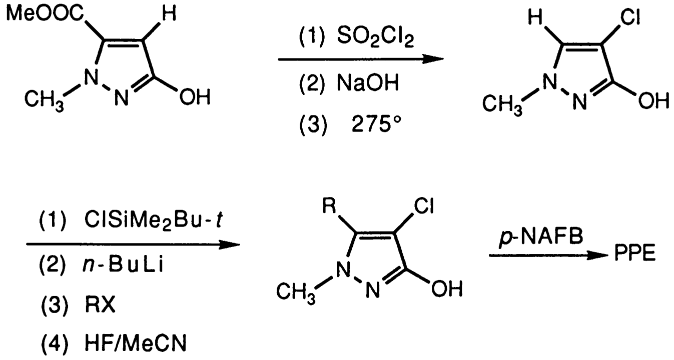

MeOOC
H
CH3
N
N
OH
(1) SO2Cl2
(2) NaOH
(3) 275°
H
Cl
CH3
N
N
OH
(1) ClSiMe2Bu-t
(2) n-BuLi
(3) RX
(4) HF/MeCN
R
Cl
CH3
N
N
OH
p-NAFB
PPE

Figure 10.

The following groups were introduced at the 5-position (electrophilic reagent given in parentheses): alkyl (alkyl halide), CHO (dimethylformamide), Cl (Cl_3CCCl_3), CH_3S (H_3CSSCH_3), F_3CS (F_3CSSCF_3), and many others.

The 4'-Position on the Phenyl Moiety. Considering substituents on the phenyl group in the pyrazole phenyl ethers discussed herein, the nitro group at the 4'-position was most critical for biological activity and was held invariant, although other electron withdrawing groups at this position, such as halogens and the cyano group *(15)* also result in herbicidally active compounds.

Variation of Phenyl 3'-Position. Of great importance was the 3'-position, the position *ortho* to the 4'-nitro group, where a great many variations could be made resulting in a wide range of active compounds of varying selectivities (Figure 11).

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

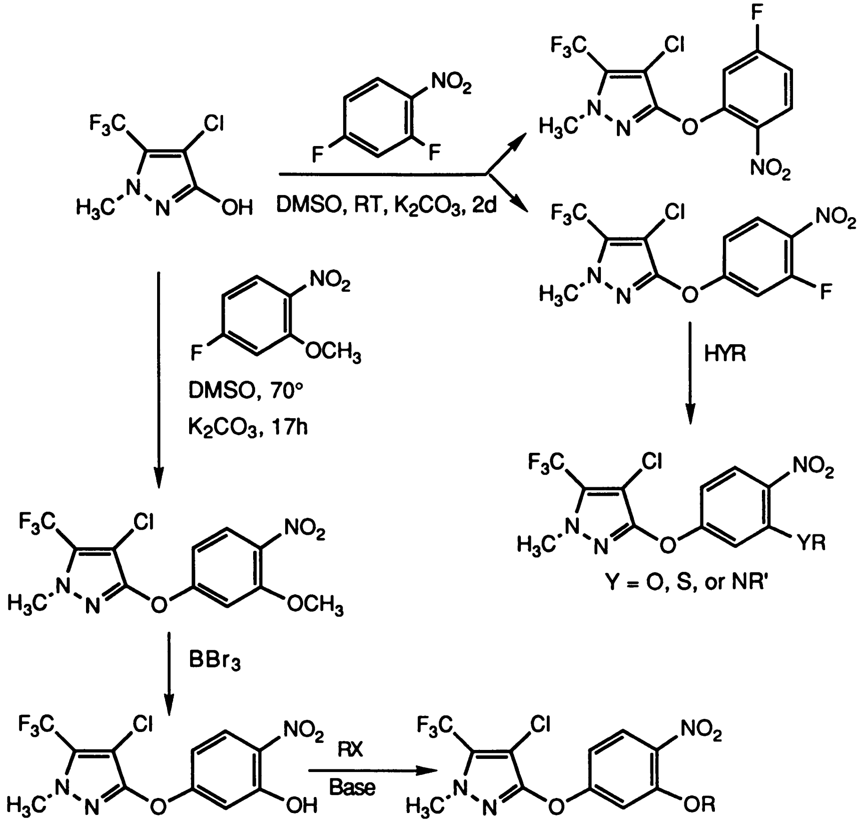


Figure 11.

Focusing on the 3'-position, it was our strategy to develop syntheses of certain key synthons from which a large variety of derivatives could be prepared by simple one step reactions. One such synthon was the 3'-

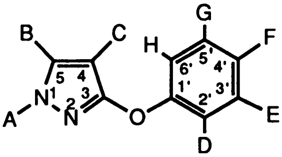
fluoro substituted PPE where the nitro activated 3'-fluoro group could be readily displaced by O, S or N nucleophiles. The reaction to prepare this intermediate resulted in a mixture of two pyrazole fluoronitrophenyl ether regioisomers from which the desired 3'-fluoro PPE was separated by fractional crystallization.

Another useful synthon was the 3'-hydroxy substituted PPE which was prepared by the sequence shown above. The 3'-OH group in this pyrazole phenyl ether could be alkylated by a variety of unsubstituted and substituted alkyl halides.

Other Substitutions on the Phenyl Moiety. The other positions on the benzene ring were of interest only to the extent that if the hydrogens at positions 2', 5' or 6' were replaced by other groups, the biological activity in most instances disappeared.

Structure/Activity Relationships

Using reactions as described above and others, a large number and variety of derivatives were prepared. Considering variation of one substituent at a time and keeping the rest of the pyrazole phenyl ether moiety constant, the following structure/activity pattern emerged for molecules of the general structure shown below.



For the substituent A, optimum activity was seen for A = CH_3; for A = H the herbicide activity decreased. As the number of carbon atoms of A was increased (A = Et, Pr, Bu), the herbicide activity decreased. Halogenating the CH_3 group (A = CF_2H, CF_2Br, CF_3) also reduced herbicide activity.

For the substituent B, the best groups were halogenated lower alkyls (B = CF_2H, CF_2Cl, CF_3, C_2F_5) and also $RS(O)_n$ (R = Me, Et; n = 0, 1, 2). Groups B conferring moderate activity were halogens; no or very little herbicide activity was seen when B = alkyl, COOR, CHO, CN.

For the substituent C, best groups were Cl, Br and CH_3; less herbicide activity was seen for C = F, NO_2, I and H; no herbicide activity was observed for COOH, CN, NH_2, SO_2R at this position.

For the substituents D, G and H, optimum herbicide activity was seen when all were hydrogens.

The substituent F in the work presented here was NO_2. When the nitro group in compounds of this type was reduced to the amino group, the herbicide activity was lost.

For the substituent E herbicide activty was seen for all kinds of C, N, O, S or P bonded organic groups resulting in a wide range of herbicide activities and selectivities.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

Summary

A new class of herbicides, pyrazole phenyl ethers, has been discovered and the structure activity of these compounds was explored in some detail. Herbicide activity was dependent on the regiochemistry of the pyrazole moiety and the nature of the substituents on the 8 sites of the parent molecule.

Literature Cited

1. DeStevens, G.; Halamandaris, A.; Wenk, P.; Dorfman, L. *J. Am. Chem. Soc.*, **1959,** *81*, 6292.
2. Lee, L. F.; Schleppnik, F. M.; Schneider, R. W.; Campbell, J. W. *J. Heterocyclic Chem.*, **1990**, *27*, 243.
3. Lee, L. F.; Moedritzer, K.; Rogers, M. D. U. S. Patent 4,855,442, 8 August 1989, Monsanto Company.
4. Gaede, B. J.; Torrence, L. L. U. S. Patent 4,984,902, 14 August 1990, Monsanto Company.
5. Hamper, B. C. *J. Fluorine Chem.*, **1990**, *49*, 123.
6. Hamper, B. C. *J. Org. Chem.*, **1988**, *53*, 5558.
7. Hamper, B. C. *Org. Syn.*, **1991**, *70*, 246.
8. Cremlyn, R. J. *Agrochemicals;* John Wiley & Sons, Ltd., Chichester, England, 1991; p 255.
9. Dill, G. M., Monsanto Agricultural Company, unpublished data.
10. Sherman, T. D.; Duke, M. V.; Clark, R. D.; Sanders, E. F.; Matsumoto, H.; Duke, S. O. *Pest. Biochem. Physiol.*, **1991**, *40*, 236.
11. Moedritzer, K.; Rogers, M. D. U. S. Patent 4,964,895, 23 Oct. 1990, Monsanto Company.
12. McBee, E. T.; Pierce, O. R.; Kilbourne, H. W.; Wilson, E. R. *J. Am. Chem. Soc.*, **1953**, *75*, 3152.
13. Aoyagi, E. I.; U. S. Patent 4,477,462, 16 Oct. 1984, Chevron Research Company.
14. Fehlauer, A; Grosz, K. P.; Slopianka, M; Sucrow, W.; Lockley, W.J. S.; Lwowski, W. *Chem. Ber.*, **1976**, *109*, 253.
15. Moedritzer, K.; Rogers, M. D. European Patent 371,947, 6 June 1990, Monsanto Company.

RECEIVED June 29, 1992

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch015

Chapter 16

N-Substituted-2,6-(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates

Synthesis and Herbicidal Activity

William F. Goure, Kindrick L. Leschinsky, Stephen J. Wratten, and John P. Chupp

New Products Division, Monsanto Agricultural Company, 800 North Lindbergh Boulevard, St. Louis, MO 63167

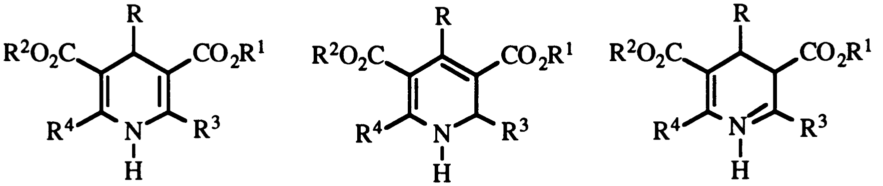
Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

The synthesis and SAR of herbicidal N-substituted-2,6-(polyfluoromethyl)-1,2-dihydropyridine-3,5-dicarboxylates is described. N-substituted dihydropyridines were readily prepared by treatment of the corresponding dihydropyridyl anions with electrophiles. Herbicidal activity of the N-substituted dihydropyridines is correlated with the rate of hydrolytic cleavage of the N-substituent to afford **2** or **3**. Dihydropyridine **2** is shown to undergo oxidation in the soil to afford herbicidal **1**, thereby relating the activity of N-substituted dihydropyridines to the corresponding aromatic herbicides.

The foundation for the discovery and development of herbicidal pyridine-3,5-dicarboxylates began in Monsanto's herbicide discovery laboratories in the early 1980s. Intensive investigations into the synthesis of novel 2,6-(haloalky)pyridine-3,5-dicarboxylates, coupled with an empirical herbicide screening effort and a dash of serendipity, bore fruit, and in 1985 Dr. L. F. Lee first described the herbicidal activity of 2,6-bis(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates (*2*). Four isomers of the dihydropyridines were shown to exhibit excellent preemergence herbicidal activity—1,4-, 3,4-, 1,2-, and 1,6-dihydropyridines (Figure 1). (In spite of formal nomenclature rules, but for the sake of consistency, the 2- and 6-positions of the pyridines and dihydropyridines are arbitrarily assigned to those pyridine ring carbons attached respectively to the difluoromethyl and trifluoromethyl groups.) Concomitant with the discovery of herbicidal dihydropyridine-3,5-dicarboxylates, Lee also discovered that the corresponding aromatic 2,6-bis(polyfluoromethyl)pyridine-3,5-dicarboxylates exhibited excellent preemergence herbicidal activity (Figure 2) (*3*).

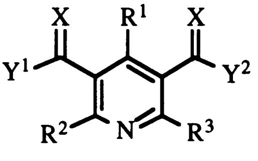
The effect of substituent modifications at all five carbon atoms of the pyridine ring upon the herbicidal activity of the aromatic 2,6-bis(polyfluoromethyl)pyridine-3,5-dicarboxylates has been extensively investigated (*2, 4-10*). These structure versus activity relationship studies demonstrated that at least one of the substituents at the 2- and/or 6-position must be a fluoromethyl group. These same studies also revealed that the substituent at the 4-position could accommodate a large variation in structural types with retention of herbicidal activity; including, phenyl, substituted, linear, and

0097–6156/92/0504–0161$06.00/0

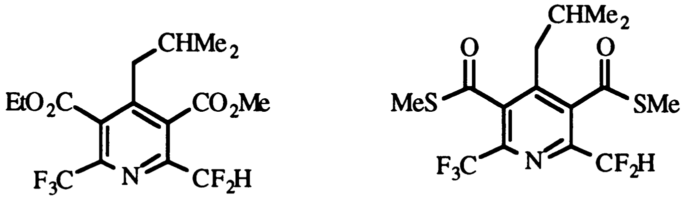


R^1 and R^2 = alkyl
R^3 and R^4 = alkyl, fluorinated methyl
R = Ph, alkyl, haloalkyl, alkoxyalkyl, alkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylalkyl, heterocycle

Figure 1. Herbicidal Dihydropyridine-3,5-dicarboxylates



R = (un)substituted alkyl, alkenyl, alkynyl, heterocyclic, cycloalkyl
R^2 and R^3 = Me, fluorinated Me, chlorofluorinated Me
X = O, imino;
Y^1 and Y^2 = H, halo, OR, SR, NHR, NR_2



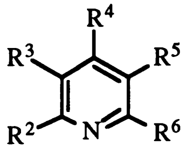
@ 0.14 kg/ha, complete barnyard grass control with cotton safety

Dimension Herbicide

Figure 2. Herbicidal 2,6-Substituted Pyridine-3,5-dicarboxylates.

branched chain alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclic moieties. An equally large variation in structural types derived from the carboxylate functionality were also found to be tolerated at the 3- and/or 5-postions. Figure 3 summarizes the range of functionality which can be accommodated by the pyridine ring with retention of herbicidal activity.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016



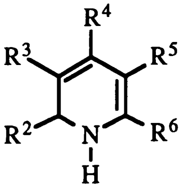
R^2 and R^6 = chlorinated, fluorinated, or chlorofluorinated Me
alkyl, alkoxy, and OH;

R^3 and R^5 = CO_2H derivatives (e.g., ester, amide, acid, aldehyde,
ketone, thioacid, thioester, nitrile, etc.)
CO_2H derived heterocycle (e.g., oxazole, thiazole, etc.),
heterocycle, (un)substituted alkyl;

R^4 = Ph, alkyl, haloalkyl, alkoxyalkyl, alkylthioalkyl,
alkylcarbonyloxyalkyl, cycloalkylalkyl, heterocycle,
halo, OR, OH, aralkyl, NHR, NR_2;

Figure 3. SAR at Carbons 2-6 for Pyridine-3,5-dicarboxylate Herbicides.

Although discovered first, the structure versus herbicidal activity relationships of the dihydropyridine-3,5-dicarboxylates have been less extensively studied, due in part to the synthetic limitations imposed by the dihydropyridine structure. Nonetheless, Chupp and coworkers (*11*) have investigated the effect of substituent changes at carbons 2-6 upon the herbicidal activity of 1,2-dihydropyridine-3,5-dicarboxylates, and have found a similar SAR to that found for the aromatic analogues (Figure 4).



R^2 and R^6 = chlorinated, fluorinated, or chlorofluorinated Me, alkyl;
R^3 and R^5 = CO_2H derivatives (e.g., ester, amide, thioacid, thioester);
R^4 = alkyl, alkoxyalkyl, alkylthioalkyl, cycloalkylalkyl, cycloalkyl;

Figure 4. SAR at Carbons 2-6 for 1,2-Dihydropyridine-3,5-dicarboxylate Herbicides.

However, despite the extensive SAR studies, the effects of incorporation and structural modifications of a nitrogen-substituent on the herbicidal activity of 2,6-bis(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates had not been investigated. Since a N-substituent was the only remaining opportunity for modifying the structure

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

versus the herbicidal activity of this new class of compounds, it became the focus of investigation. The results of that investigation are reported herein.

A priori, the herbicidal activity of the dihydropyridine-3,5-dicarboxylates could be attributed to one of three different phenomenon. First, the dihydropyridine-3,5-dicarboxylates could be inherently herbicidally active. Alternatively, the herbicidal activity of the dihydropyridines could be due to their decomposition, in the soil or *in vivo*, via dehydrohalogenation to afford herbicidal aromatic pyridine-3,5-dicarboxylate analogues. Indeed, dehydrohalogenation followed by hydrogen migration of dihydropyridine-3,5-dicarboxylates to afford herbicidally active pyridine-3,5-dicarboxylates has been found by Lee and coworkers to be a facile process in the presence of amine and alkoxide bases and has been utilized for the synthesis of the aromatic analogues (*12*). Finally, the activity of the dihydropyridines could be due to their direct oxidation, either in the soil or *in vivo*, to the corresponding aromatic pyridines. These alternatives are schematically depicted in Figure 5.

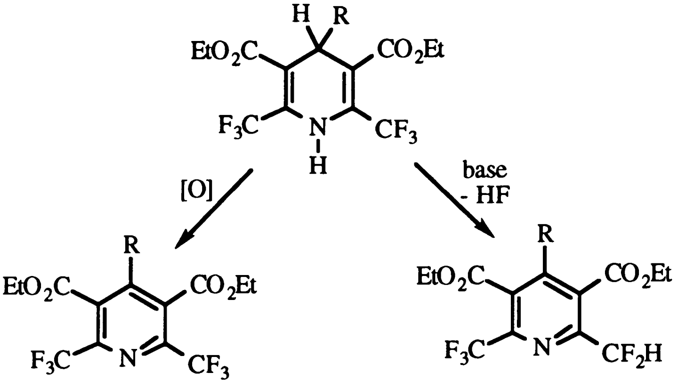


Figure 5.

On the basis of SAR studies comparing the herbicidal activity of 2,6-bis-(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates to the corresponding aromatic 2,6-bis(polyfluoromethyl)pyridine-3,5-dicarboxylates (*2, 3, 11*) it was postulated that the activity of dihydropyridine-3,5-dicarboxylates is due to direct oxidation, either in the soil or *in vivo*, to the herbicidally active pyridine-3,5-dicarboxylates. On the basis of this postulate, we investigated the preparation and biological activity of N-substituted dihydropyridines in hopes of obtaining pro-herbicides with more desirable physical properties (water solubility, volatility, soil residual, etc.) than the corresponding aromatic pyridines. Thus it was postulated, that following application, cleavage of the N-substituent, either in the soil or *in vivo*, would release the N-H dihydropyridine, which following oxidation, would yield the herbicidally active pyridine.

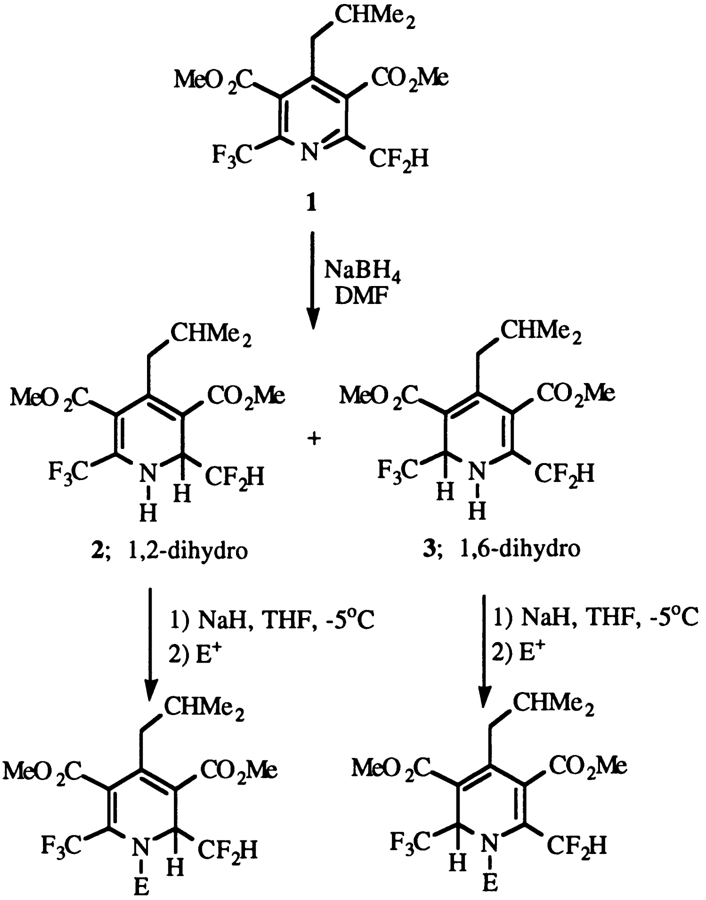
Results and Discussion.

Synthesis. The synthesis of N-substituted dihydropyridine-3,5-dicarboxylates is depicted in Figure 6. Utilizing standard methodology, sodium borohydride reduction of dimethyl 2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)pyridine-3,5-dicarboxylate (**1**) in DMF affords approximately a 50/50 mixture of 1,2- and 1,6-dihydropyridines **2** and **3** (*2*), which can be readily separated by silica gel chromatography on a preparative scale (>50 g). The 1,2-dihydropyridine isomer

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

proved to be more easily purified than the 1,6-isomer, thus most of the analogues prepared were N-substituted-1,2-dihydropyridines. Only a limited number of N-substituted-1,6-dihydropyridines were prepared for comparative purposes.



E = alkyl, acyl, benzoyl: 30-85%

Figure 6. Synthesis of alkyl, acyl, and benzoyl N-substituted Dihydropyridine-3,5-dicarboxylates

Treatment of the purified 1,2- or 1,6-dihydropyridines with NaH followed by reaction of the resulting dihydropyridyl anion with electrophiles afforded the corresponding N-substituted dihydropyridines in good to excellent yield (*13*). Lee and coworkers have previously reported (*12*) that treatment of 2,6-bis(polyfluoromethyl)-dihydropyridine-3,5-dicarboxylates with amine or alkoxide bases results in the elimination of hydrogen fluoride followed by hydrogen rearrangement to afford the corresponding aromatic pyridines. In contrast, the sodium salts of **2** and **3** were found to be surprisingly stable. Thus, relatively unreactive electrophiles such as cyclopropylmethylbromide were successfully reacted with the requisite sodium salts of **2** and **3** in refluxing THF with no evidence for dehydrohalogentation and subsequent aromatization. Furthermore, interconversion of the sodium salts of **2** and **3** did not occur under the reaction conditions. Presumably, the stability of **2** and **3** is due to the irreversibility of the NaH mediated metalation which prevents anion rearrangement and subsequent dehalogenation (*12*).

In contrast to the success found with simple alkyl and acyl electrophiles, attempted preparation of N-carbamyldihydropyridine-3,5-dicarboxylates via reaction of the sodium salts of **2** and **3** with isocyanates failed. However, reaction of the sodium salt of **2** with phosgene afforded carbamylchloride **4** which upon treatment with ammonia or amines gave the corresponding ureas in good to excellent yield (Figure 7).

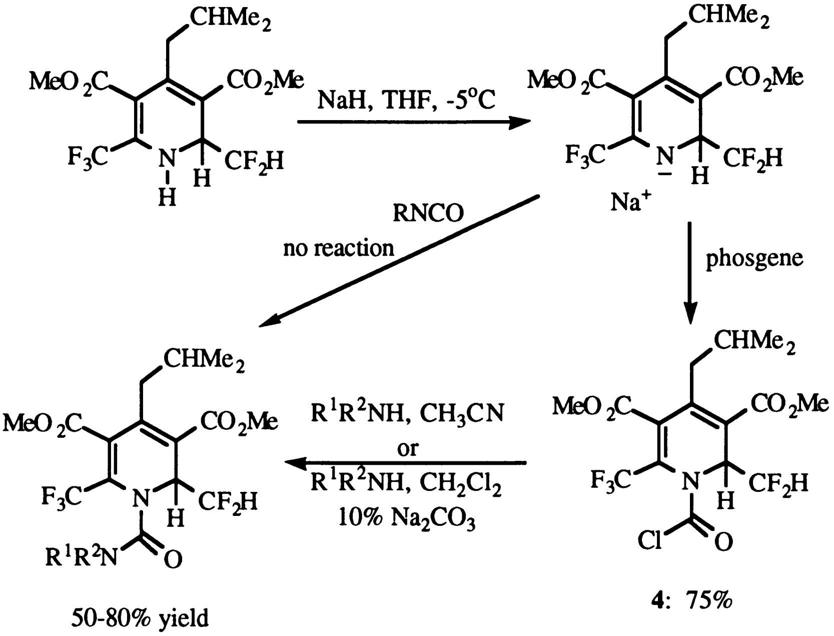
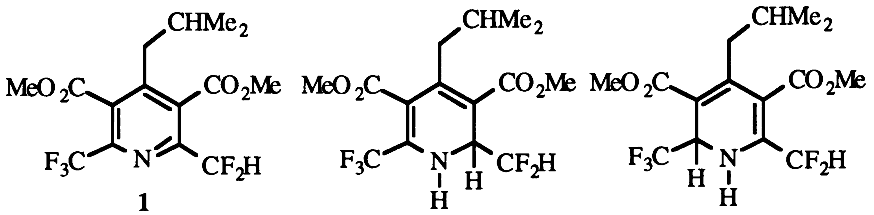


Figure 7. Synthesis of N-carbamyldihydropyridine-3,5-dicarboxylates

Herbicidal Activity. Throughout this discussion, preemergence herbicidal activity will be expressed as a narrow leaf weed GR80 (WGR80 in lb/acre) which is the amount of herbicide, averaged over five narrow leaf weed species (downy brome, proso millet, barnyard grass, large crap grass, and green foxtail), required to inhibit 80% of weed growth relative to that of the untreated control. For comparative purposes, Figure 8 shows the herbicidal activity of the standards utilized in this study: dimethyl 2-(difluoromethyl)-4-isopropyl-6-(trifluoromethyl)-pyridine-3,5-dicarboxylate (**1**) and the corresponding 1,2- and 1,6-dihydropyridine isomers (**2** and **3**).

The first series of compounds examined were the N-alkyl dihydropyridine-3,5-dicarboxylates, which displayed moderate herbicidal activity (Table I, compounds **5** - **9**), although they were less active than the corresponding unsubstituted dihydropyridines or aromatic pyridine (Table I, compounds **1** - **3**). The N-alkyl substituents in compounds **5** - **9** would generally not be expected to be readily cleaved, either in the

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016



1
WGR80 = 0.01-0.04 lb/acre

2
1,2-dihydro
WGR80 = 0.03 lb/acre

3
1,6-dihydro
WGR80 = 0.03 lb/acre

Figure 8.

soil or *in vivo*. Thus, the herbicidal activity of **5** - **9** could be interpreted as resulting from the inherent activity of the N-substituted-dihydropyridine-3,5-dicarboxylates. However, the activity of **5** - **9** is also consistent with partial cleavage of the N-substituent as shown in Figure 9 to afford low concentrations of the corresponding unsubstituted dihydropyridines. Thus, for example in the case of **5**, S_N2 displacement of the N-alkyldihydropyridine by nucleophiles (e.g. H_2O) would afford the dihydropyridinium anion as a leaving group, which, upon proton abstraction from water, would yield **2** or **3**. Alternatively, **6** - **9** could afford **2** or **3** via a S_N1 process involving the intermediacy of the stabilized methylthiomethyl, cyclopropylmethyl, and benzyl carbenium ions. Both of these processes would be facilitated due to the electron withdrawing carboxy and fluorinated alkyl groups on the dihydropyridine ring which would stabilize the resultant dihydropyridinium anion. We sought to test these possibilities by incorporating substituents which would be expected to be less susceptible to S_N2 and/or S_N1 displacement based on steric and electronic

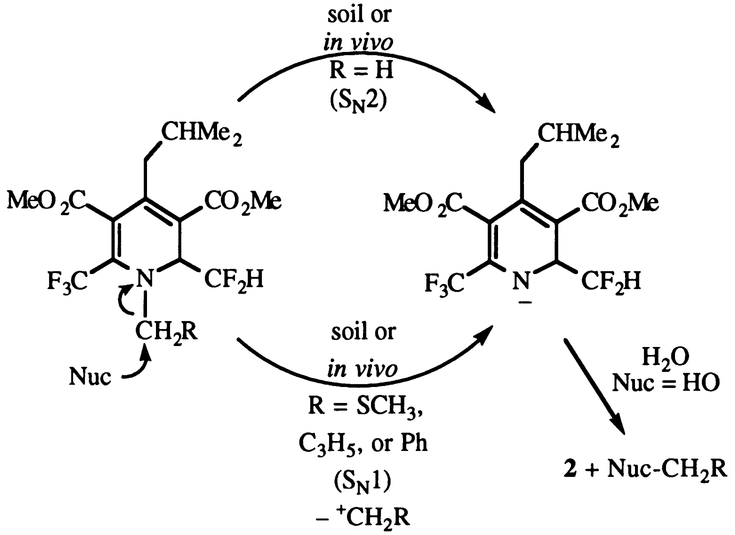


Figure 9.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

Table I. Percent yield, structure and herbicidal activity of alkyl-, acetyl-, and benzoyl-substituted dimethyl 2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-1,2-dihydropyridine-3,5-dicarboxylates

compound	% yield	N-substituent	narrow leaf weed GR80 (lb/acre)
1		—	0.03
2		H	0.04
3*		H	0.04
5#		CH_3	0.15
6	31	CH_2SCH_3	0.22
7*		CH_2SCH_3	0.61
8	8.3	$CH_2(C_3H_5)$	0.52
9	58	$CH_2(C_6H_5)$	0.97
10	68	$COCH_3$	1.12
11*	19	$COCH_3$	0.18
12	52	$COCH_2CH_3$	0.95
13	68	$COCH(CH_3)_2$	4.24
14	62	$COCH_2F$	0.04
15	55	$COCHF_2$	0.05
16		$COCH_2Cl$	0.06
17	50	$COCHCl_2$	0.06
18	53	$COCCl_3$	0.05
19	6	$COCH_2Br$	0.13
20	80	$COCH_2OCH_3$	0.17
21	35	$COCH_2OC_6H_5$	0.30
22	62	$COCHCHCH_3$	0.16
23	77	CO*p*-$(NO_2)C_6H_4$	0.65
24*	37	CO*p*-$(NO_2)C_6H_4$	0.06
25*	84	COC_6H_5	0.47

#51/49 mixture of 1,2- and 1,6-dihydropyridine isomers.
*1,6-Dihydropyridine isomer.

considerations. However, attempts to prepare N-isopropyl or N-neopentyl analogues to prevent N-substituent cleavage failed.

N-acetyl substituted dihydropyridines were the next series of compounds to be examined, and exhibited a large range of herbicidal activity. Those compounds with electron donating or weakly electron withdrawing substituents attached to the acetyl carbon possessed only moderate herbicidal activity (**10** - **13**, and **20** - **21**). For these compounds, a decrease in herbicidal activity was observed with an increase in steric bulk at the acetyl carbon. Thus, replacing an ethyl group in **12** with an isopropyl group in **13** resulted in a 4-fold decrease in herbicidal activity. Electronic factors also affect the herbicidal activity of the N-acetyl dihydropyridines. Thus, replacing OMe in **20** with halogen resulted in an increase in herbicidal activity that is proportional to the electronegativity of the halogen (**20** < **19** < **16** < **14**). A similar trend is found with **12** and **22**, in which the increased electronegativity of an sp^2 hybridized carbon compared to an sp^3 hybridized carbon is postulated to lead to the observed increased activity. Incorporation of two or more halogens, however, did not further increase herbicidal activity (**15**, **17**, **18**). The halogenated N-acetyl dihydropyridines **14** - **18** all exhibited essentially identical herbicidal activity, which was also equivalent to that of **1**, **2**, or **3**, despite rather substantial changes in both steric and electronic environments surrounding the acetyl carbon. These results are most consistent with **14** - **18** breaking down to a common, herbicidally active moiety.

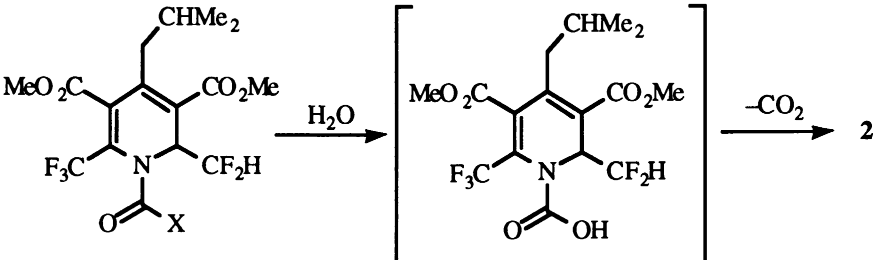
Amide hydrolysis normally requires rather harsh conditions (*14*). Therefore, facile cleavage of the N-acetyl substituent from the compounds in Table 1 might not be expected. However, the fluorinated alkyl and carboxyl groups on the dihydropyridine ring greatly stabilize the dihydropyridyl anion thereby facilitating hydrolytic cleavage of the N-acetyl group. This is the most consistent explanation of the SAR displayed by the compounds shown in Table 1. The herbicidal activity of these compounds is proportional to the predicted rate of hydrolysis of the N-acetyl group based on a consideration of Taft's E_s and σ^* values (*15*). Thus, the decrease in herbicidal activity as hydrogens are replaced with methyl groups parallels the predicted decreased rate of hydrolysis based on both steric and polar parameters. This same trend is found for the halogenated and oxygenated N-acetyl compounds, although it is less straightforward due to contradictory steric and electronic effects for these substituents. Additionally, the activity of **24** compared to **25** is proportional to the predicted rate of hydrolytic cleavage of the benzoyl groups.

Thus, we propose that the herbicidal activity of the compounds in Table 1 is a result of cleavage, either in the soil or *in vivo*, of the N-substituent to afford herbicidally active **2** or **3**. Those N-substituted dihydropyridines containing more labile substituents (e.g., **15**, **17**, **18**) are cleaved more rapidly and afford higher concentrations of **2** or **3**, therefore displaying greater herbicidal activity. In contrast, those compounds containing more robust N-substituents (e.g., **8**, **9**, **13**) undergo less N-substituent cleavage and afford lower concentrations of **2** or **3**, and as a result show less herbicidal activity. When the rate of cleavage of N-substituted dihydropyridine-3,5-dicarboxylates is sufficiently rapid (e.g., **15**, **16**, **18**), the concentration of **2** or **3** will be equal to that of the applied N-substituted dihydropyridine, and thus the herbicidal activity cannot exceed that of **2** or **3**.

The final series of compounds to be studied were the N-acyl dihydropyridine-3,5-dicarboxylates shown in Table 2. Hydrolytic cleavage of the N-substituent to afford herbicidal **2** also explains the activity of **4** and **26** (Table 2). Upon exposure to dilute aqueous acid, **4** is readily hydrolyzed to **2**, presumably via the intermediacy of the corresponding carbamic acid **27** which losses CO_2 to afford **2** (Figure 10). Rapid hydrolysis of **26** to **2** is consistent with the known ability of azole amides to readily hydrolyze (*16*), and accounts for the fact that the herbicidal activity of **26** is comparable to that of **2**.

Ethylcarbamate **28** and phenylthiocarbamate **29** exhibit moderate herbicidal activity. In contrast, phenylcarbamate **30** failed to exhibit any herbicidal activity. Although **29** and **30** would be predicted to be less susceptible to hydrolysis than **28** (*17*), thereby accounting for their reduced herbicidal activity, the total lack of herbicidal activity for **30** cannot be readily explained. Moreover, thioesters are more slowly hydrolyzed than the corresponding oxy esters (*17*), thus the herbicidal activity of **29**

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016



X = Cl; **4**
X = 1-pyrazole; **26**

27

Figure 10.

and **30** is the reverse of that predicted on the basis of hydrolysis arguments. We currently do not have an explanation for these results.

The herbicidal activity of the N-carbamyl compounds in Table 2 might also, on cursory examination, be considered inconsistent with N-substituent cleavage to afford herbicidally active **2** or **3**. However, primary and secondary carbamic esters and ureas are known to undergo based induced hydrolysis via an elimination-addition mechanism (Figure 11) rather than an addition-elimination mechanism that is common for esters and tertiary carbamic esters and ureas (*18*). The SAR for the N-carbamyl dihydropyridines in Table 2 is consistent with loss of the N-substituent by such a process. Thus, N,N-dimethylcarbamyl dihydropyridine **43**, which lacks an abstractable hydrogen on nitrogen, is 500 to 1000-fold less active than the other analogues in Table 2. In the case of alkyl substituents (compounds. **33** - **40**) little change in activity was found with structural variations. The acetic acid analogue **41** was less active, as would be expected for a compound with two acidic protons. Since the carboxylic acid proton is more acidic than the N-H proton (*18*), cleavage of the N-substituent would be predicted to be reduced due to the proximity of a carboxylate anion to the base abstractable N-H. The reduced herbicidal activity of *tert*-butyl analogue **42** is also in keeping with known effects of steric hindrance upon the rate of elimination of carbamic esters and ureas (*18*). The anilino-carbamyl N-substituted dihydropyridines **44** - **50** all exhibited essentially identical herbicidal activity despite

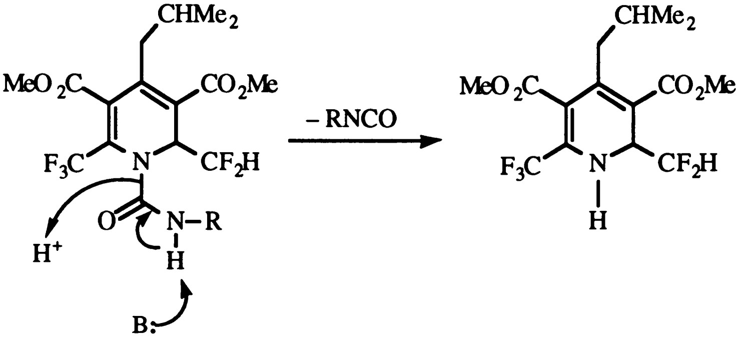


Figure 11.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

rather substantial steric and electronic changes. This is again most consistent with **44** - **50** breaking down to a common, herbicidally active moiety. Thus, as was the case with alkyl and acetyl N-substituted dihydropyridine-3,5-dicarboxylates, the herbicidal activity of the ureas in Table 2 is most readily rationalized by cleavage of the N-substituent to give **2** or **3**.

Table 2. Percent yield, structure and herbicidal activity of N-acyl dimethyl 2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-1,2-dihydropyridine-3,5-dicarboxylates

compound	% yield	N substituent	narrow leaf weed GR80 (lb/acre)
4	75	COCl	0.02
26	81	CO-1-pyrazole	0.02
28*	84	CO_2Et	1.28
29	80	$COSC_6H_5$	2.58
30	65	$CO_2C_6H_5$	inactive
31	89	$CONH_2$	0.26
32*	26	$CONH_2$	0.05
33	78	$CONHCH_2CH_3$	0.01
34*	75	$CONHCH_2CH_3$	0.13
35	72	$CONHCH_2CHCH_2$	0.05
36	62	$CONHCH(CH_3)CH_2CH_3$	0.05
37	83	$CONHOCH_3$	0.06
38	69	$CONHCH_2CH(OCH_3)_2$	0.06
39	66	$CONHCH_2C_6H_5$	0.06
40	51	$CONHCH_2CO_2CH_3$	0.07
41	71	$CONHCH_2CO_2H$	3.69
42	81	$CONHC(CH_3)_3$	1.69
43	56	$CON(CH_3)_2$	11.22
44	71	$CONHC_6H_5$	0.06
45	67	$CONH(4\text{-}OCH_3C_6H_4)$	0.03
46	61	$CONH(3\text{-}OCH_3C_6H_4)$	0.05
47	69	$CONH(3\text{-}CH_3C_6H_4)$	0.05
48	62	$CONH(3\text{-}CF_3C_6H_4)$	0.03
49	65	$CONH[3,5\text{-}(CF_3)_2C_6H_3]$	0.02
50	57	$CONH(2\text{-}FC_6H_4)$	0.06
51	61	$CON(C_2H_5)C_6H_5$	1.00

*1,6-Dihydropyridine isomer.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

The last structure versus herbicidal activity relationship that can be commented on, based on the compounds studied, concerns the 1,2- versus the 1,6- dihydropyridine isomers. However, comparison of the herbicidal activity of analogous 1,2- and 1,6-dihydropyridine isomers fails to reveal a consistent trend (Tables 1 and 2). Although, in general the 1,2-dihydropyridine isomers were less active than the 1,6-isomers, several exceptions exist. Thus, in the case of compounds **6** and **7** and **33** and **34**, the 1,2-dihydropyridine isomers were more efficacious than the 1,6-isomers. However, compounds **10** and **11**, **23** and **24**, and **31** and **32** exhibited the reverse relationship.

Although the SAR results are consistent with the conclusion that the N-substituted dihydropyridines studied were functioning as pro-herbicides and decomposed in the soil or *in vivo* to afford herbicidally active **1**, **2**, or **3**, additional supporting evidence was sought. Unambiguous evidence for the rapid decomposition of various N-substituted dihydropyridines to **2** was obtained by HPLC, HPLC/MS and ^{1}H-NMR studies. Thus, **14** (WGR80 = 0.04 lb/acre) was stable in acetonitrile for 6 days without decomposition as judged by HPLC/MS. However, addition of pH 10 buffer resulted in rapid disappearance of **14** (within one day) and the concomitant appearance of **2** (Figure 12). In contrast, in the presence of pH 10 buffer, N-dimethylcarbamyl dihydropyridine **43** (WGR0 = 11.22 lb/acre) was unchanged after three weeks as determined by HPLC/MS.

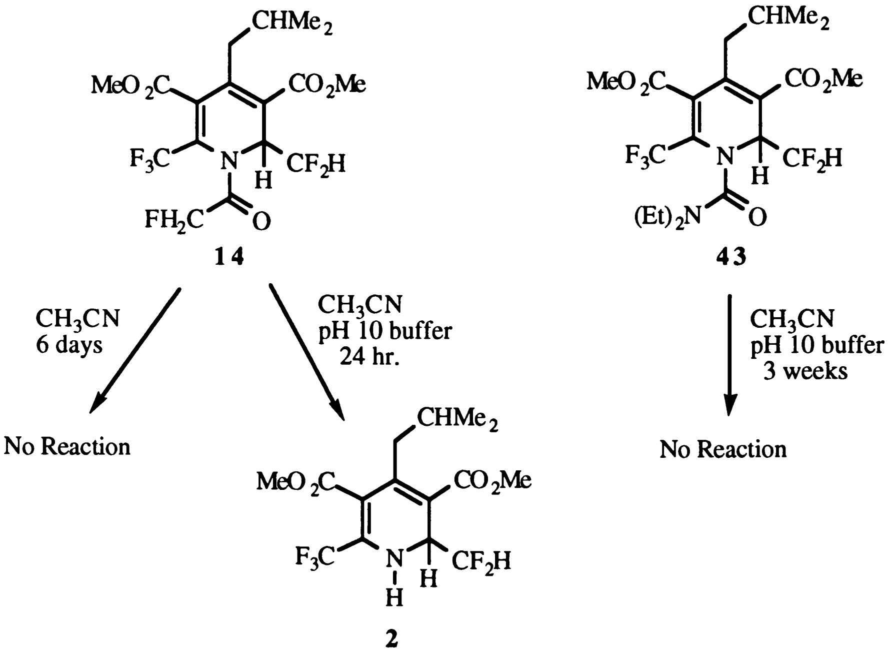
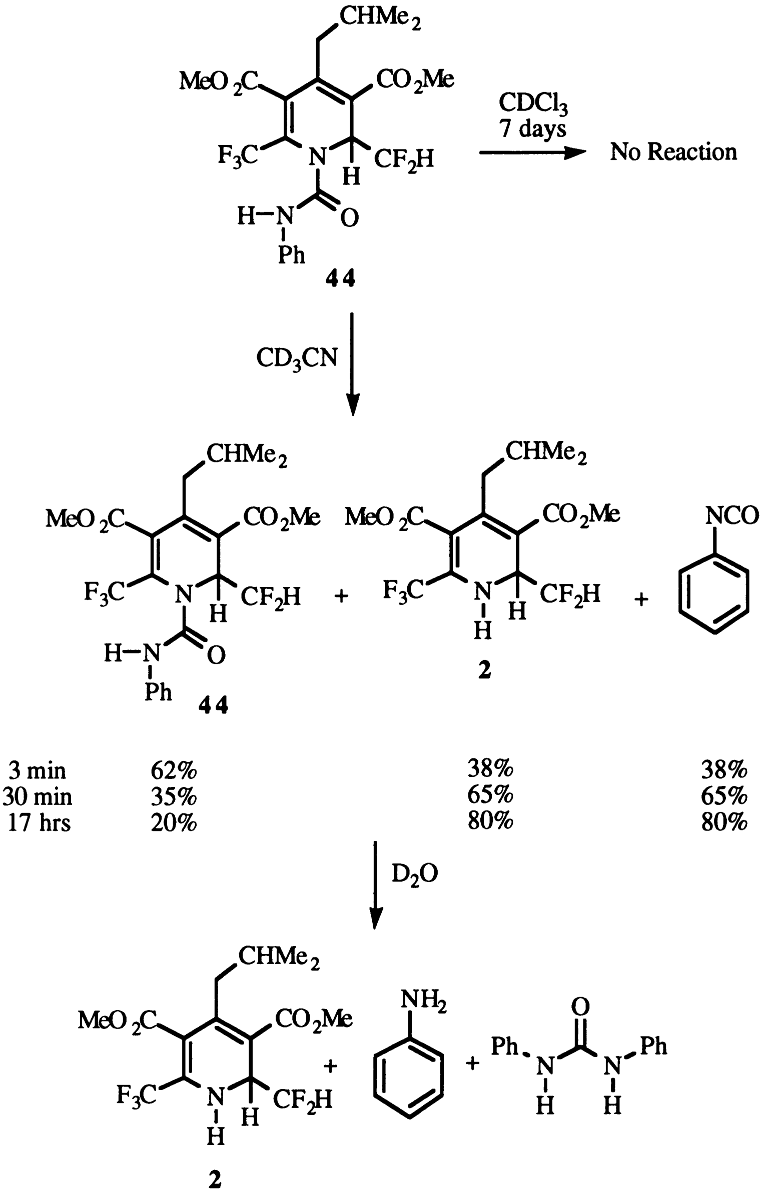


Figure 12.

Initially confusing and apparently contradictory results were obtained when ureas such as **44** were analyzed by ^{1}H-NMR in different solvents (Figure 13). In $CDCl_3$ solution, **44** was unchanged after storage for a week at room temperature. In contrast, when CD_3CN was used as the solvent, **2** and a corresponding amount of phenyl

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016



3 min	62%	38%	38%
30 min	35%	65%	65%
17 hrs	20%	80%	80%

Figure 13.

isocyanate were detected within minutes. Within three minutes after dissolution in CD_3CN, 38% conversion to **2** was measured by NMR integration. After 30 minutes, 65% decomposition to **2** had occurred, and after 17 hours, only 20% unchanged **44** remained (80% decomposition to **2**). When D_2O (50 μl) was added to the 17-hour mixture, followed by incubation at room temperature for an additional 5 days, the remaining 20% of **44** was found to have to degraded to **2**. Additionally, the phenyl isocyanate liberated upon decomposition of **44** was hydrolyzed to a mixture of aniline and phenylurea.

The above results suggested that under acidic conditions, breakdown of the aryl ureas such as **44** should be retarded. Indeed, **44** and **48** were found to be stable for several hours in pH 3 - 4 buffer when analyzed by HPLC, but were unstable at pH 6 and above (Table 3). After 22 hours at pH 3, essentially all of **44** remained, but only 26% of **48** remained. These results are consistent with the increased acidity of the N-H proton due to the presence of the electron withdrawing CF_3 group in **48**. The acidity of the N-H proton is decreased in unsubstituted or alkyl-substituted ureas, such as **31** and **33**, thus accounting for increased stability of **31** and **33** at pH 6 compared to **44** and **48**.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

Table 3. Stability of Urea Analogues in Solutions of Different pH as Determined by HPLC Analysis

pH	age of solution (hr)	% **31** remaining	% **33** remaining	% **44** remaining	% **48** remaining
3	2-3	98	100	100	95
3	22-24			100	26
4	3-5	98	100	97	91
4	22-24			74	4
5	5-6	98	100	52	15
5	22-24	88			
6	6-8	83	100	6	0
6	22-24		97		
7	7-9	14	91	0	0
8	10	0	44		
9	11	0	8		

One final set of experiments was conducted to directly determine the fate of N-substituted dihydropyridines and N-H dihydropyridines in aged, treated soils. Each of eight compounds (Table 4) was mixed with soil, and this soil was added as a cover layer to unseeded pots containing untreated soil beneath. The amount of each compound used corresponded to a nominal 11 lb/acre application rate. The pots were then placed in the greenhouse for seven days. The pots were then sampled and the amounts of applied compound and **1** and **2** were determined.

Although the experiment could have been improved by more sampling over time and by more thorough accounting of all of the applied herbicide in each pot, the results were qualitatively conclusive. The major component detected in the extracts of soils treated with dihydropyridines displaying high herbicidal activity was **1**. Pyridine **1** was clearly formed from **2**, the N-acetyl dihydropyridine **14**, and from aryl ureas such as **44**, **45**, and **48**. In these cases, very little to none of the applied compound was present seven days after treatment. The amount of **1** recovered from these treatments was approximately the same as from the pots which had been treated directly with **1**, and this amount represented only about 20% of the applied concentration; the remainder presumably having been lost to volatilization. These results are consistent with the hypothesis that the N-substituted dihydropyridines, in the soil, undergo N-substituent cleavage to give **2** (or **3**) which undergoes oxidative conversion to **1**.

Table 4. Products Recovered from Soil Treated with Dihydropyridines and Aged Seven Days in the Greenhouse

Compd.	narrow leaf weed GR80 (lb/acre)	Compd. Conc. in soil 7 DAT (ppm)	1 Conc. in soil 7 DAT (ppm)	2 Conc. in soil 7 DAT (ppm)
1	0.03	13	13	0
2	0.04	0	11	0
14	0.04	0	8	0
31	0.26	60	19	9.5
33	0.01	152	1.8	12
44	0.06	13	9	1.2
45	0.03	1.1	20	1.6
48	0.03	1.2	7.5	0
51	1.0	106	0	0

In contrast to the results of the aryl ureas, the ethyl urea **33** and the unsubstituted urea **31** were still present in the soil in large amounts at seven days, accompanied by smaller amounts of **1** and **2**. The decomposition of these compounds was much slower than the aryl analogs. However, in the case of **31**, the concentration of **1** was comparable to that of the control, thereby accounting for its high herbicidal activity. Thus, these results support the idea that alkyl ureas represent "chemical-timed-released" forms of the herbicidally active pyridine **1**. The disubstituted urea, **51**, which possessed low herbicidal activity, was still present in large amounts in the seven-day old soil, but in this case, no **1** or **2** were detected. This result is consistent with the idea that facile loss of the N-substituent is required for formation of herbicidally-significant levels of **1** or **2** in the soil.

Little can be said about the rates of decomposition of the N-substituted dihydropyridines or **2** itself from this data since sampling at early time points was not conducted. We can speculate that the degradation may have been quite rapid since the residual levels of **1** were essentially identical to each other and to the level resulting from direct application of **1**.

Conclusions

The results of these studies have established a credible explanation for the herbicidal activity of N-substituted dihydropyridine-3,5-dicarboxylates. It was demonstrated that N-unsubstituted 1,2-dihydropyridines undergo oxidation in soil to readily regenerate aromatic pyridines with known herbicidal activity. When the nitrogen atom is substituted with acyl or certain other substituents, these groups can be lost with unexpected ease, regenerating the unsubstituted dihydropyridine, which can in turn yield the pyridine. Apparently, the electron-withdrawing ability of the two adjacent fluoroalkyl groups makes the dihydropyridyl anion a very good leaving group,

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

allowing these normally stable amide bonds to hydrolyze readily in polar organic solvents or with mild base. The stability of the N-substituted dihydropyridines parallels the trends in their herbicidal activity. When soil, which had been treated with various N-substituted dihydropyridines, was aged for seven days in the greenhouse and extracted, it was possible to completely explain the pattern of herbicidal activity on the basis of the compounds' abilities to regenerate **1** in the soil.

Acknowledgments

We are thankful to Dr. Martin Mahoney, Dr. Allan Ciha, and Ms. Cheryl Wilen for providing the necessary herbicidal activity data.

Literature Cited

1. Goure, W. F.; Leschinsky, K. L.; Wratten, S. J.; Chupp, J. P. *J. Agri. Food Chem.*, **1991**, *39*, 981.
2. Lee, L. F. (to Monsanto Company), Eur. Pat. Appl. EP 135,491 (Mar. 27, 1985); *Chem Abstr.* **1985**, *103*, 178173s.
3. Lee, L. F. (to Monsanto Company), Eur. Par. Appl. EP 133,612 (Feb. 27, 1985); *Chem Abstr.* **1986**, *104*, 19514h.
4. Lee, L. F. (to Monsanto Company) U.S. Patent 4,692,184.(September 8, **1987**).
5. Lee, L. F. (to Monsanto Company) U.S. Patent 4,741,766 (May 3, **1988**).
6. Lee, L. F. (to Monsanto Company) U.S. Patent 4,826,530 (May 2, **1989**).
7. Lee, L. F.; Miller, M. L. (to Monsanto Company) U.S. Patent 4,655,816 (April 7, **1987**).
8. Lee, L. F.; Miller, M. L. (to Monsanto Company) U.S. Patent 4,698,093 (October 6, **1987**).
9. Lee, L. F.; Miller, M. L. (to Monsanto Company) U.S. Patent 4,835,279 (May 30, **1989**).
10. Lee, L. F.; Sing, Y. L. (to Monsanto Company) Eur. Pat. Appl. EP 278,944 (August 17, 1988); *Chem. Abstr.* **1988**, *109*, 230818.
11. Chupp, J. P.; Lee, L. F.; Goure, W. F.; Molyneaux, J. M. (to Monsanto Company) U.S. Patent 4,908,057 (March 13, **1990**).
12. Lee, L. F.; Stikes, G. L.; Molyneaux, J. M.; Sing, Y. L.; Chupp, J. P.; Woodard S. S. *J. Org. Chem.* **1990**, *55*, 2872.
13. Stout, D. M.; Meyers, A. I. "Recent Advances in the Chemistry of Dihydropyridines". *Chem. Rev.*, **1982**, *82*, 223, and references cited therein.
14. Ogliaruso, M. A.; Wolfe, J. F. "The Synthesis of Carboxylic Acids and Esters and their Derivatives". In *The Chemistry of Acid Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, **1979**; Chapter 7.
15. Shorter, J. "The Separation of Polar, Steric, and Resonance Effects in Organic Reactions by the Use of Linear Free Energy Relationships". *Quart. Rev. (London)*, **1970**, *24*, 433.
16. Staab, H. A. "New Methods of Preparative Organic Chemistry IV. Syntheses Using Heterocyclic Amides (Azolides)". *Angew. Chem. Internat. Edit.*, **1962**, *1*, 351.
17. Janssen, M. J. "Thiolo, Thiono and Dithio Acids and Esters". In *The Chemistry of Carboxylic Acids and Esters*, Patai, S., Ed.; Interscience-Publishers: New York, **1969**; Chapter 15.
18. Williams, A.; Douglas, K. T. "Elimination—Addition Mechanisms of Acyl Transfer Reactions". *Chem. Rev.* **1975**, *75*, 627.

RECEIVED March 19, 1992

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch016

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

Chapter 17

5-Substituted-2,4-imidazolidinediones

Synthesis and Herbicidal Activity

Siok-Hui Wee and Michael P. Prisbylla

**Organic Synthesis Department, ICI Americas Inc., 1200 South 47th Street,
P.O. Box 4023, Richmond, CA 94804–4023**

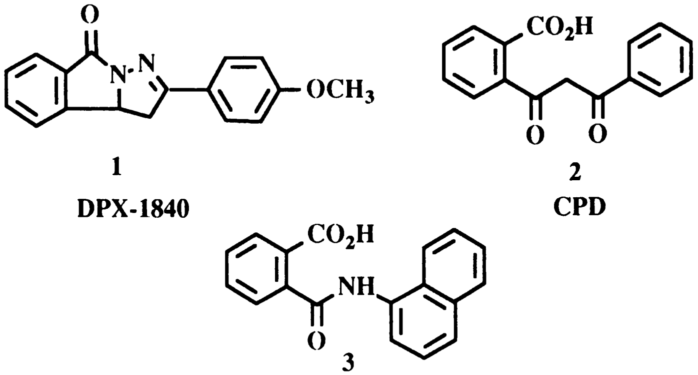
Two isomeric forms of 5-substituted-2,4-imidazolidinediones have been found to have herbicidal properties. Novel, efficient and unambiguous synthetic routes to these isomeric materials are described. Their structure activity relationships and crop selectivity patterns are discussed.

The relationship between aromatic moieties within a given molecule producing a given biological response is intriguing. Critical to the maintenance of this spatial relationship is the role of the connecting group of atoms. Not only must the tertiary structure be maintained by this connecting group, but it must not introduce substituents detrimental to activity. A number of molecules possess these attributes. Well known materials include the auxin transport inhibitors (Figure 1) such as DPX-1840 (*1*) and ring opened isomers (*2*), Naptalam (NPA) (*3*), 1-(2'-carboxyphenyl)-3-phenylpropane-1,3-dione (CPD) and related materials (*4*). They contain a required 2-carboxyphenyl moiety connected to another aromatic ring via a conjugated or planar system of atoms (*5*). While the distance between the aromatic groups center to center has an optimum, it does not appear necessary that they be in the same plane and that numerous bridging groups have been found to be acceptable (*6,7*).

Compounds possessing auxin transport activity often display negative root geotropism on whole plants and have been associated with herbicidal properties. Examples include NPA, analogs of CEPIQ (*8,9*), benzoxazolylbenzoates and other related materials (*10-13*). Molecules that maintain portions of this relationship include the sulphonylureas (*14,15*) and benzoylureas. Clearly, subtle differences are producing rather dramatic changes with regard to the target sites of these materials.

We were interested in pursuing relationships of this type, wanting to use small ring heterocycles to orient two aromatic moieties in space. The connecting heterocycles chosen were 5-heteroatom substituted 2,4-imidazolidinediones (*16*). The desired 3-aryl, 4 and 1-aryl, 5 materials are shown in Figure 2 and were chosen because of their ease of synthesis, known herbicidal properties (*17-19*) and our previous interest in this area (*20-23*). Of particular interest was the potential effect of the heteroatom, X, linking the aromatic moieties. A heteroatom at this position would allow numerous low energy conformations to become available, thereby increasing the likelihood of obtaining biological activity.

0097–6156/92/0504–0177$06.00/0

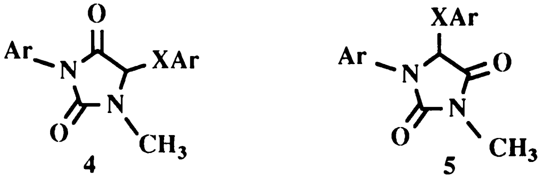


1
DPX-1840

2
CPD

3
NPA

Figure 1. Known Auxin Transport Inhibitors



4

5

Figure 2. Isomeric 2,4-Imidazolidinediones

Synthesis

The initial route for the preparation of the desired imidazolidinediones is shown in Figure 3. This route was based on the displacement of the mesylate obtained from the hydroxy derivatives **8** or **9** with various nucleophilies. The desired 5-hydroxy-2,4-imidazolidinediones were obtained via the condensation of the phenyl ureas with glyoxylic acid (*18*). Unfortunately, this condensation is not regiospecific, often affording mixtures of **8** and **9**. Even when pure regioisomers were obtained, uncertainty remained as to their structural assignments and also as to which isomer was the active component. To alleviate these problems, unambiguous syntheses of the desired materials were devised.

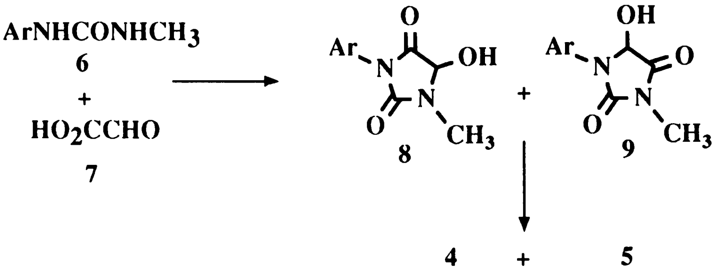


Figure 3. Initial Synthetic Route to 4 and 5

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

5-Substituted-3-Phenyl-2,4-Imidazolidinediones. Imidazolidinediones are often viewed retrosynthetically as being prepared from glycinamides and carbonyl reagents (*24,25*) such as phosgene or carbonyldiimidazole (CDI). The glycinamide required for the N-3-aryl diones was obtained by N-aryl chloroacetamide alkylation of the corresponding alkyl amine, with cyclization by CDI occurring as expected (Figure 4). Bromine in acetic acid cleanly affords the brominated materials **13**, which were readily displaced with various nucleophiles.

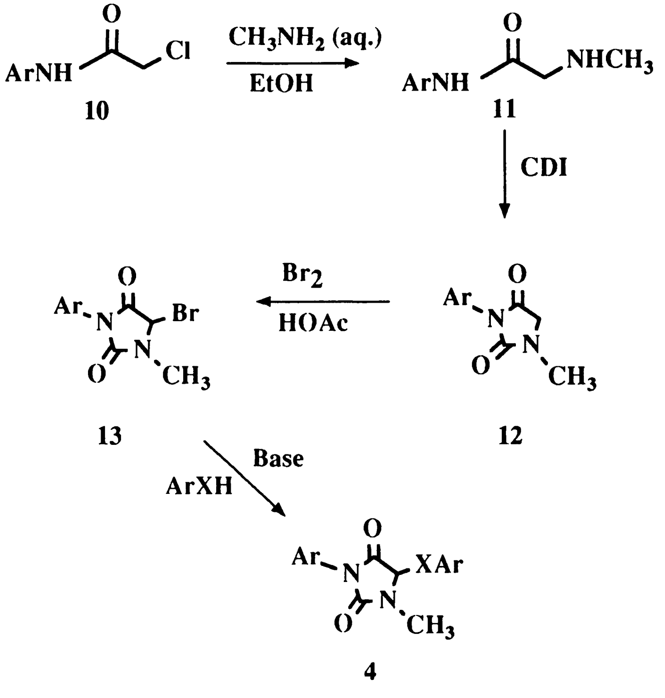


Figure 4. Unambiguous Synthesis of 4

5-Substituted-1-Phenyl-2,4-Imidazolidinediones. The isomeric substituted 1-phenyl- 2,4-imidazolidinediones **16** were prepared using a similar strategy with the important change in substitution on the glycinamide, thereby reversing the substitution pattern on the final product (Figure 5). Alkylation (NaH, KI, THF) of trifluoroacetylated anilines **14** with the chloroacetamides leads to the intermediate trifluoroacetylated glycinamides **15**. These materials were then cyclized to the imidazolidinediones **16** with additional base (NaH). On occasion, some cyclization to **16** occurred during the alkylation. It was found that the diones could be obtained directly by running the reaction in methyl ethyl ketone (MEK), with K_2CO_3 as base. This novel reaction proceeds via the presumed loss of fluoroform with yields in the 45 to 85% range. Bromination (Br_2, HOAc) and displacement with thiols, in this case, were much more difficult reactions, perhaps reflecting increased steric congestion about the five position. The capricious yields for the two steps were quite low, in the 20 to 40% range.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

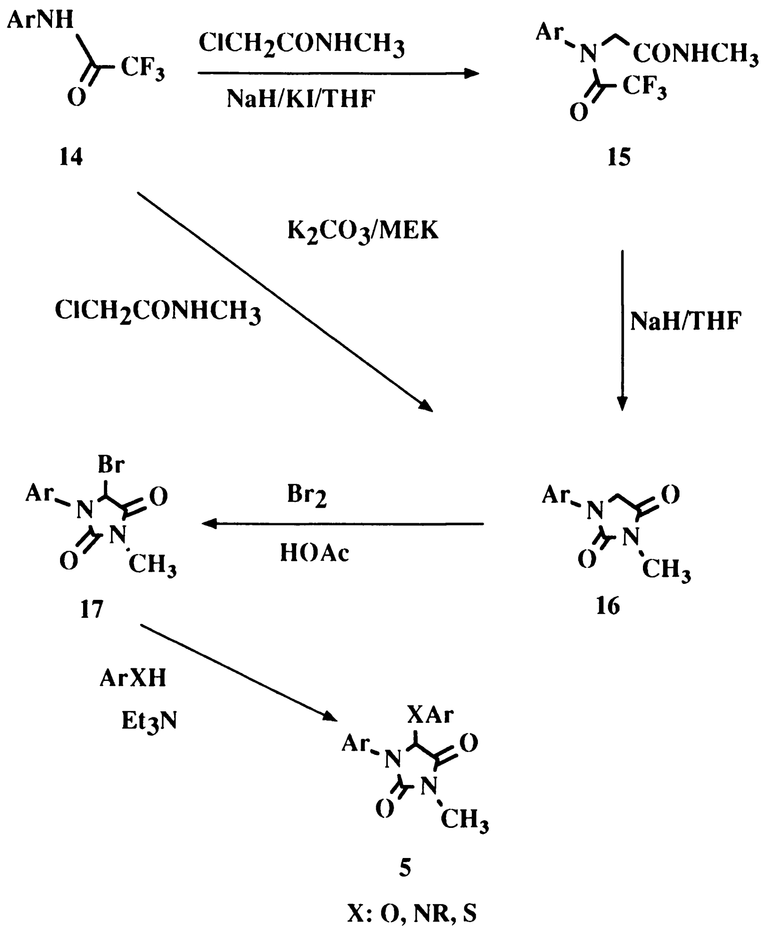

ArNH
CF3
O
14
ClCH2CONHCH3
NaH/KI/THF
Ar
N
CONHCH3
CF3
O
15
K2CO3/MEK
ClCH2CONHCH3
NaH/THF
Br
Ar
N
O
N
O
CH3
17
Br2
HOAc
Ar
N
O
N
O
CH3
16
ArXH
Et3N
XAr
Ar
N
O
N
O
CH3
5
X: O, NR, S

Figure 5. Unambiguous Synthesis of 5

Biological Activity

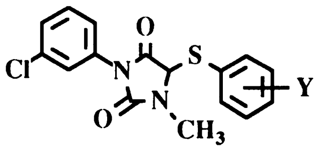
The imidazolidinediones were tested in the greenhouse on a variety of grass and broadleaf weeds, both pre- and postemergent. The grass weeds included downy brome (*Bromus tectorum*), green foxtail (*Setaria viridis*), annual ryegrass (*Lolium multiflorum*), watergrass (*Echinochloa crusgalli*), shattercane (*Sorghum bicolor*), wild oat (*Avena fatua*) and broadleaf signalgrass (*Brachiaria platyphylla*) and are reported as the combined average of grasses (AVG). The broadleaf weeds were annual morningglory (*Ipomoea pururea*), velvetleaf (*Abutilon theophrasti*), sicklepod (*Cassia obtusifolia*) and wild mustard (*Brassica kaber*) and are reported as the combined average of the broadleaves (AVB). The crops were soybean (*Glycine max*, SOY), wheat (*Triticum aestivum*, WH), rice (*Oryza sativa*, RC), sugarbeet (*Beta vulgaris*, SB), corn (*Zea mays*, CN) and cotton (*Gossypium hirsutum*, COT).

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

Structure–Activity Relationships

The synthesis program began using the N-3-aryl-2,4-imidazolidinediones because of their ease of synthesis and focused on variation of the phenyl moiety connected to the heteroatom. Sulfur was chosen as the connecting heteroatom because of its high reactivity in the displacement reaction. It was found, however, that phenyl substitution produced little response in terms of overall activity. Alkyl substitution on nitrogen (N-1) optimized with methyl, as even ethyl substitution produced a substantial reduction in activity (data not shown). These compounds are, as seen from the data in Table I, primarily broadleaf active materials, in both pre- and post-emergent applications.

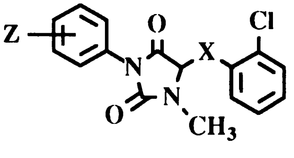
Table I. Biological Activity with Phenyl Substitution



Compound	Y	RATE(kg/ha)	AVG (Pes/Poes)	AVB
18	H	4.0	73/43	91/99
19	4-F	4.0	82/47	73/100
20	2-Cl	4.0	80/23	65/100
21	2-CH_3	4.0	73/27	98/45
22	2-OCH_3	4.0	73/40	98/91

The Connecting Heteroatom. With this basis, we set out to optimize the connecting heteroatom between the imidazolidinedione and aryl group, using 2-chlorophenyl as a standard aromatic moiety connected to the heteroatom. The data in Table II, using 3-chlorophenyl subsitituiton on the imidazolidinedione, reveals the poor activity obtained with nitrogen as the connecting heteroatom. Whether nitrogen was alkylated or not had very little effect on the herbicidal activity (data not shown). That thio substitution was optimal is seen with 3-(4-chlorophenyl) substitution on the dione. Here an oxygen heteroatom produces quite weak activity (25 vs 26).

Table II. Variation of Biological Activity With The Connecting Heteroatom

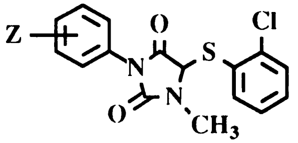


Compound	Z	X	Rate(kg/ha)	AVG (Pes/Poes)	AVB
20	3-Cl	S	4.0	80/23	65/100
23	3-Cl	NH	4.0	17/0	71/55
24	3-Cl	O	4.0	53/57	63/88
25	4-Cl	O	4.0	0/20	0/86
26	4-Cl	S	4.0	57/48	71/95

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

N-3 Phenyl Substitution. Our attention turned to substitution on the imide N-phenyl (Table III). Large groups, such as 2-CF_3 (**27**) and 2-OCH_3 (**28**) were particularly disfavored, affording inactivity. Unsubstituted phenyl (**29**) and 2-Cl (**30**) were active, but the highest levels of activity was obtained with 2-F (**31**). This indicates a preference for small *ortho* substituents and thus 2-carboxy substitution was not pursued. The *meta* position produced good activity with CF_3 (**32**), while *para* substitution (**26**,**33**,**34**,**35**) afforded poor activity. Disubstitution was based on using 2-F but did not increase activity when combined with substituents in the four position (CH_3 (**36**), F (**37**), Cl (**38**)). Substantial activity was seen with 3-F,4-CH_3 (**39**) prompting the preparation of 2,5-difluorophenyl **42** (26, 27). This substitution pattern afforded activity similar to **31** and thus a comparison between the two was made (Table IV). These materials are active both pre- and postemergence, mainly on broadleaf weeds. The major difference between them is the substantial loss of crop selectivity with 2,5-difluorophenyl substitution.

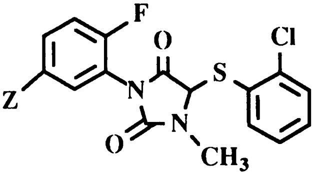
Table III. Biological Activity With N-3 Phenyl Substitution



Compound	Z	Rate(kg/ha)	AVG (Pes/Poes)	AVB
20	3-Cl	1.00	12/0	62/24
26	4-Cl	0.50	27/-	36/-
27	2-CF_3	4.00	0/0	0/0
28	2-OCH_3	4.00	0/0	0/0
29	H	1.00	50/0	80/74
30	2-Cl	4.00	78/27	88/37
31	2-F	0.25	13/17	91/83
32	3-CF_3	1.00	20/19	91/73
33	4-CH_3	0.50	0/4	10/34
34	4-OCH_3	1.00	0/0	7/12
35	4-F	0.50	33/0	24/47
36	2-F,4-CH_3	0.50	0/0	35/0
37	2,4-DiF	0.50	0/0	46/10
38	2-F,4-Cl	0.50	0/10	42/64
39	3-F,4-CH_3	1.00	37/38	100/94
40	2-F,5-CF_3	1.00	53/54	38/81
41	2-F,5-NO_2	4.00	0/0	45/45
42	2,5-DiF	0.25	29/6	56/94

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

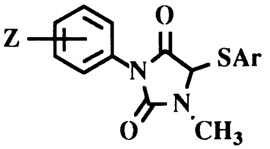
Table IV. Crop Selectivity



Compound	Z	RATE kg/ha		AVG	AVB	SOY	WH	RC	SB	CN	COT
31	H	0.25	Pes	13	91	80	25	50	70	30	15
		0.25	Poes	17	83	30	0	0	95	0	0
42	F	0.50	Pes	60	92	100	80	70	100	40	70
		0.25	Poes	6	92	70	0	30	100	10	20

Thio(heterocyclic) Five Position Substitution. Previously it had been demonstrated (see Table I) that there was little response in the variation of substituents on the phenylthio moiety in the five position. The effect of other heterocyclic moieties on the herbicidal activity was still in question. A number of diverse heterocycles were introduced into this position using sulfur as the connecting atom. The data in Table V indicates that two other substituents, 2-pyridinyl (43) and 2-pyrimidinyl (44), offer levels of activity similar to 2-chlorophenyl. However, when these heterocycles were combined with 2-fluorophenyl substitution in the three position, there was no increase in activity (49 and 50).

Table V. Biological Activity With Heteroaromatic Substitution

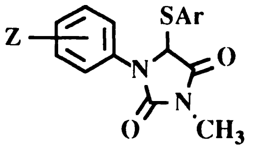


Compound	Ar	Z	RATE kg/ha	AVG (Pes/Poes)	AVB
20	2-Chlorophenyl	3-Cl	0.50	0/0	25/0
43	2-Pyridinyl	3-Cl	0.50	49/28	71/82
44	2-Pyrimidinyl	3-Cl	0.50	0/27	64/61
45	2-(1H-Methylimidazolyl)-	3-Cl	0.50	0/14	56/58
46	2-(1H-Benzimidazolyl)-	3-Cl	0.50	0/0	0/74
47	2-(5-Chloropyrimidinyl)-	3-Cl	0.50	26/-	12/-
48	2-(4-Phenyl)thiazolyl	3-Cl	1.00	34/64	20/0
49	2-Pyridinyl	2-F	0.50	35/40	76/90
50	2-Pyrimidinyl	2-F	0.50	52/41	79/91

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

Isomeric 1-Phenyl-2,4-Imidazolidinediones. The isomeric 2,4-imidazolidinediones were of interest because they would substantially alter the relative positioning of the two aromatic moieties. It was assumed that these isomeric materials would be acting at the same site as the N-3-aryl isomers and thus the previously optimized substituents were used. Unfortunately, the data in Table VI reveals substantially lower levels of activity. If the above assumptions are correct, then it would appear that further distance between the two aromatic moieties, as obtained in the N-3-aryl isomers, is preferred.

Table VI. Biological Activity of 1-Aryl-5-Substituted-2,4-Imidazolidinediones



Compound	Ar	Z	RATE kg/ha	AVG (Pes/Poes)	AVB
51	2-Chlorophenyl	2-F	0.25	55/0	65/85
52	2-Pyridinyl	2-F	0.25	45/0	76/64
53	2-Chlorophenyl	2,5-DiF	0.25	10/0	28/15
54	2-Pyrimidinyl	2,5-DiF	0.25	0/17	65/0

Mode of Action

The injury effected by these materials on the leaves of susceptible species was yellow chlorosis. This injury is reminiscent of urea-like activity and was not similar to that displayed by auxin transport inhibitors. Therefore, Hill reaction inhibition results were obtained to determine if these compounds are photosystem II inhibitors. The compounds are not inhibitors in this assay and no further effort was made to determine their mode of action.

Conclusions

The use of models as an aid for the design of novel herbicides, though not leading to similar modes of action, can still provide new bioactive molecules. These isomeric imidazolidinediones prepared and evaluated here are primarily broadleaf herbicides for grass crops, with activity levels in the 1/4 to 1/2 kg/ha range.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch017

Acknowledgments

The authors wish to acknowledge the helpful discussions of W. J. Michaely in the preparation of this manuscript.

Literature Cited

1. Beyer, E. M., Jr. *Plant Physiol.* **1972**, *50*, 322-327.
2. Beyer, E. M., Jr.; Johnson, A. L.; Sweetser, P. B. *Plant Physiol.* **1976**, *57*, 839-841.
3. Katekar, G. F.; Geissler, A. E. *Plant Physiol.* **1977**, *60*, 826-829.
4. Brown, B. T.; Johansen, O.; Katekar, G. F.; Sasse, W. H. F. *Pestic. Sci.,* 1973, *4*, 473-484
5. Katekar, G. F.; Geissler, A. E. *Plant Physiol.,* **1980**, *66*, 1190-1195.
6. Smith, G.; Kennard, C. H. L.; Katekar, G. F. *Aust. J. Chem.*, **1983**, *36*, 2455-2463.
7. Teitei, T. *Agric. Biol. Chem.*, **1983**, *47*, 1461-1465.
8. D'Amico, J. J., U. S. Patent 4,097,260, 1978.
9. Gardner, G.; Semple, J. E. *J. Plant Growth Regul.*, **1990**, *9*, 161-169.
10. Baum, J. S.; Chen, T. M., U. S. Patent 4,659,360, 1987.
11. Baum, J. S.; Chen, T. M., U. S. Patent 4,556,411, 1985.
12. Baum, J. S.; Chen, T. M., U. S. Patent 4,623,379, 1986.
13. Brouwer, G. B.; MacPherson, E. J.; Ames, R. B.; Neidermyer, R. W.; Crittendon, C. E. U. S. Patent, 4,035,175, 1977.
14. Levitt, G. In *Pesticide Chemistry: Human Welfare and the Environment;* Miyamato, J.; Kearney, P. C., Eds.; Pergamon Press, New York, 1983, Vol 1, pp 243-250.
15. Levitt, G. In *Synthesis and Chemistry of Agrochemicals;* Baker, D. R.; Fenyes, J. G.; Moberg, W. K., Eds.; ACS Symposium Series 443; American Chemical Society, Washington, DC, 1991, pp 16-31.
16. Wee, S. H. H.; Prisbylla, M. P., U. S. Patent 4,871,391, 1989.
17. Thibault, T. D.; St. Clair, R. L., U. S. Patent 4,345,936, 1982.
18. Moser, H.; Vogel, C., U. S. Patent 3,818,032, 1974.
19. Mine, A.; Fujinami, A.; Kameda, N.; Hino, N.; Satomi, T.; Tateshi, K., U. S. Patent 3,846,441, 1974.
20. Wee, S. H. H., U. S. Patent 4,977,270, 1988.
21. Prisbylla, M. P., U. S. Patent 4,859,228, 1989.
22. Prisbylla, M. P., U. S. Patent 4,911,748, 1990.
23. Prisbylla, M. P., U. S. Patent 4,958,028, 1990.
24. Bateman, J. H., *Kirk-othmer Encycl. Chem. Technol.*, **1980**, *12*, 692-711.
25. Ware E. *Chem. Rev.*, **1950**, 403.
26. Krenzer, J.; Stach, L. J., U. S. Patent 4,758,263, 1988.
27. Gardner, G.; Pilgram, K. H.; Brown, L. J.; Bozarth, G. A. *Pest. Biochem. Physiol.*, **1985**, *24*, 285-297.

RECEIVED April 9, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

Chapter 18

Cyanoacrylate Inhibitors of Photosynthetic Electron Transport

Structural Requirements for Inhibitor Potency and Herbicidal Activity

John L. Huppatz, Helen G. McFadden, Marie-Luise Huber, and Leslie F. McCaffery

Commonwealth Scientific and Industrial Research Organisation, Division of Plant Industry, Canberra 2601, Australia

Readily synthesized derivatives of 2-cyanoacrylic acid are potent inhibitors of photosynthetic electron transport. The structural features associated with optimum activity in this class of inhibitor are described with particular emphasis on the steric factors involved. Generally, inhibition of the Hill reaction correlates well with post-emergence herbicidal activity, though a series of highly active inhibitors devoid of herbicidal activity was discovered.

Photosynthesis is a particularly attractive target for the design of potential commercial herbicides. It has the obvious advantage of being a metabolic function unique to higher plants and certain bacteria, with no counterpart in mammalian physiology. Compounds specifically blocking the photosynthetic process might therefore be expected to present minimal toxicological problems. Furthermore, the complexities of photosynthesis have been largely unraveled and the structure of the reaction center at the molecular level is now known in considerable detail.

Several sites for interference with the photosynthetic process have been identified but by far the largest group of photosynthetic herbicides act by inhibiting photosynthetic electron transport at photosystem II (PSII). These compounds, which include the urea, triazinone and uracil herbicides (*1*), owe their phytotoxicity to an ability to bind to a 32 kD polypeptide (the D1, or Q_B protein) in the PSII reaction center in chloroplasts. This type of PSII inhibitor displaces the native plastoquinone, Q_B, from its binding site, thereby blocking electron flow and initiating a chain of events which ultimately results in plant death (*2*).

The PSII herbicide binding site has shown an intriguing affinity for a wide range of chemically diverse structures, a property which makes rationalization of the structure/activity relationships between the different herbicide classes difficult (*3*,*4*). The susceptibility of the PSII site to a wide range of chemical types has resulted in a steady flow of new structures with herbicidal properties in recent years. Paradoxically, no new PSII inhibitor herbicide has made a significant impact on world agriculture for many

0097–6156/92/0504–0186$06.00/0

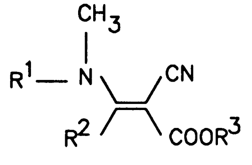
Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

years. The reasons for this are complex but include the continued effectiveness and low cost of established PSII herbicides, particularly the urea and triazine families, and the inability of most PSII inhibitors to match the field performances of other modern herbicides, particularly the sulfonylureas. Theoretically, there is no known reason why PSII inhibitor herbicides could not approach the low dose rates characteristic of the sulfonylureas (*5*). This is particularly true for highly potent inhibitors of photosynthetic electron transport, provided properties of foliar penetration and transport within plant tissue were favorable.

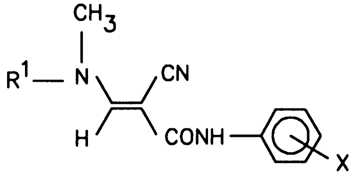
Compounds based on 2-cyanoacrylic acid esters were first reported as herbicides in 1969-71 in a series of patents (*6-8*), but little information was given on the spectrum of activity and the mode of action was not discussed. A detailed study of compounds of general structure **1** (*9*) revealed that herbicidal activity was associated with N-methylanilino cyanoacrylates **1**, [R^1=phenyl, R^2=H, and R^3=simple alkyl (2-4 carbon atoms)] and that phytotoxicity apparently resulted from inhibition of photosynthetic electron transport (*9*). Subsequently, structure **1** was modified to produce vinylogous ureas of general structure **2** (*10*). These compounds had similar structural requirements to the original series on the "left-hand side" of the molecule (a β-hydrogen atom and an N-methylanilino function) and the same stereochemistry. They were also inhibitors of the Hill reaction; a property accounting for the potent phytotoxicity of some members of the series (*10*).

The most potent compounds in the 2-cyanoacrylate series were found to be compounds with quite different structural features from the N-methylanilino analogues **1** and **2**. Significantly, they are characterized by a *cis* orientation of the amino and carbonyl functions as shown in general structure **3**. Moreover, in contrast to the N-methyl-N-aryl analogues **1** and **2**, they incorporate a hydrogen atom attached to the enamine nitrogen and a β-substituent R^2 that is other than hydrogen. With favorable substitution at R^1, R^2 and R^3, 2-cyanoacrylates **3** are extraordinarily potent inhibitors of photosynthetic electron transport. Moreover, the activity of these molecules was found to be highly sensitive to minor structural variation thereby providing significant insight into the topography of the binding site occupied by the inhibitors (*11-16*).

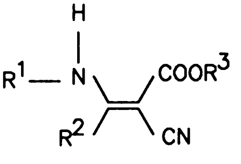
This review will summarize the structural requirements of 2-cyanoacrylates **3** associated with potent inhibition of photosynthetic electron transport and highlight features which provide some understanding of the topographical limits to the binding of this type of molecule.



1



2



3

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

Chemistry.

Synthetically, cyanoacrylates are readily accessible with a range of substituents possible for each of R^1, R^2 and R^3. Initially compounds were prepared by a two-step procedure involving the formation of an ethoxymethylene compound **4** from the appropriate cyanoacetic ester and a triethyl (or trimethyl) *ortho* ester followed by reaction with an appropriate amine to give compounds of general structure **3** [Figure 1, route (a)].

Two important limitations restrict the usefulness of this reaction pathway as a completely general synthetic method. Firstly, the range of *ortho* esters commercially available or conveniently prepared is limited, thereby restricting the versatility of the reaction with respect to R^2. Secondly, the reaction either failed or gave very modest yields when applied to cyanoacetamides, thereby severely restricting the range of possible analogues.

The most obvious alternative procedure involved acylating a cyanoester or amide, followed by methylation of the enol form of the acyl derivative. The Rathke and Cowan procedure (*17*) for the acylation of acetoacetic and malonic esters was successfully extended to cyanoacetic esters and amides. This method involved condensation of a cyanoacetic ester or amide and an acid chloride in the presence of triethylamine and anhydrous magnesium chloride [Figure 1, route (b)] resulting in excellent yields of the

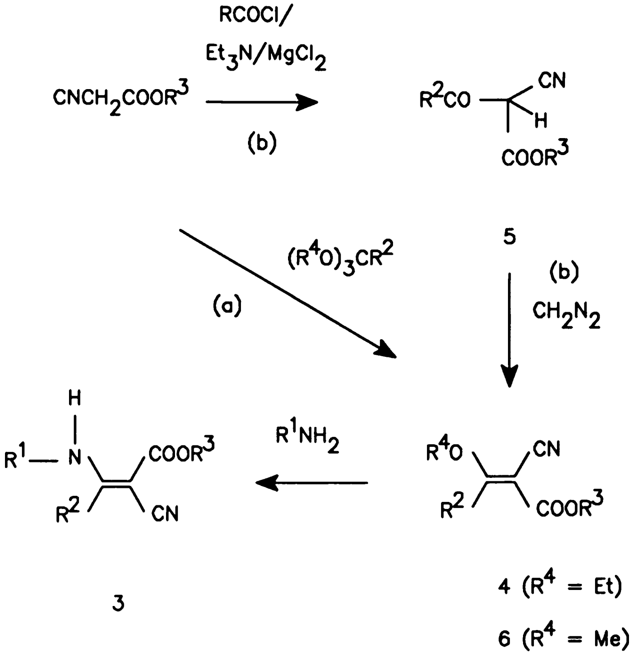


Figure 1

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

acylated product **5**. The methoxymethylene intermediates **6** were obtained by facile methylation of the acyl derivatives with ethereal diazomethane. Reaction with amines, either directly or in refluxing acetonitrile, completed this alternative synthesis of cyanoacrylates **3**.

The stereochemistry of the 2-cyanoacrylates **3** is an important determinant of biological activity. Compounds in this series have a *Z*-configuration (i.e. a *cis* orientation of the amino and ester functions), although compounds unsubstituted in the β-position **3** (R^2=H) can exist as either geometric isomer (*13*). The latter compounds are at best weak inhibitors of the Hill reaction and have little or no herbicidal activity.

Stereochemistry was assigned from spectral (PMR and infrared) data (*13*,*18*) and supported by an x-ray structure determination of one of the more potent inhibitors **3** (R^1=4-chlorobenzyl; R^2=*iso*propyl; R^3=ethoxyethyl) (*18*). The x-ray data confirmed the *Z*-stereochemistry and demonstrated the presence of a planar core stabilized by a strong intramolecular hydrogen bond between the ester carbonyl oxygen and the hydrogen atom attached to the enamine nitrogen (*18*).

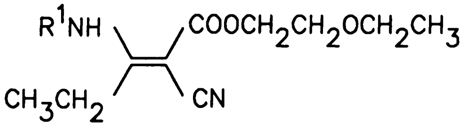
Structural Requirements for Hill Reaction Activity.

Optimization of structure **3** to achieve maximum potency in inhibiting photosynthetic electron transport was achieved by systematically varying the substituents R^1, R^2 and R^3. The intrinsic activity of each analogue was rapidly and reliably assessed using the Hill reaction in isolated pea chloroplasts. Compounds were assayed for Hill inhibition activity using chloroplast fragments isolated from the leaves of *Pisum sativum*, the electron acceptor being the blue dye, 2,3',6-trichlorophenolindophenol. The activity was expressed as pI_{50}, i.e. $-\log_{10}I_{50}$, where I_{50} was the molar concentration required to decrease the level of dye reduction to 50% of that obtained in the absence of the compound. While Hill reaction data do not necessarily correlate well with whole plant activity, a significant *in vitro* inhibition is a prerequisite for *in vivo* phytotoxicity. Other factors, such as leaf penetration, translocation and detoxification in plant tissue, ultimately determine whole plant performance and species selectivity. However, from the viewpoint of establishing the structural features necessary to maximize affinity for the binding site, the Hill reaction provides valuable insights and, when combined with glasshouse screening data, enables useful design rules to be formulated.

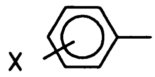
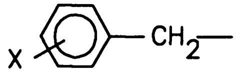
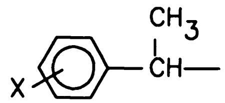
For inhibition of photosynthetic electron transport the nitrile function is mandatory; replacement by hydrogen, acyl, amide or ester (*9*) groups eliminates activity. The ester group may be replaced by an amide or keto function though these analogues are not as effective, either as Hill inhibitors or as herbicides, and will not be considered further.

The substituent R^1. With compounds of general formula **4**, significant activity can be achieved with diverse lipophilic groups (Table I). Studies with straight-chain alkyl substituents (*11*,*12*) suggested that the alkyl group was interacting with a large, unconstrained hydrophobic area in the thylakoid membrane and increased activity was associated with the increased lipophilic nature of R^1. With alkylamino-2-cyanoacrylates 3 (R^1=C_nH_{2n+1}, R^2=H, R^3=$CH_2CH_2OCH_2CH_3$), the pI_{50} increased by 0.5 unit with each additional methylene group, suggesting that inhibitors of this type partition into the membrane as they would into octanol (*12*).

Table I. Activity of Compounds of General Formula (4) as Inhibitors of the Hill Reaction



(4)

Compound No	R^1	pI_{50}
5	$n\text{-}C_8H_{17}\text{-}$	7·15
		
6	X = H	4·80
7	X = 4Cl	5·75
8	X = 2Cl	4·45
		
9	X = H	6·20
10	X = 4Cl	8·70
11	X = 2Cl	5·85
		
12	racemate	6·65
13	S–(+) isomer	7·10
14	R–(–) isomer	4·90

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

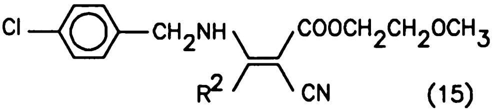
However, with compounds in which a phenyl ring was incorporated into R^1, lipophilic interactions were modified by steric effects (*14*). Phenylamino derivatives (e.g. compounds **6-8**, Table I) were relatively weak inhibitors, though activity could be increased markedly by 3- or 4-substitution (e.g. compound **7**). Inclusion of a methylene group between the phenyl and amino functions (compound **9**) resulted in an activity increase much greater than would have been expected on the basis of increased lipophilicity alone. Substitution in the phenyl ring can significantly affect Hill activity, with an increase in potency of up to 300-fold observed with a favorable substituent (e.g. compound **10**). Simple QSAR analyses of substituted phenylamino- and benzylamino 2-cyanoacrylates showed a high degree of correlation between lipophilicity of the substituent and activity (*19*). Moreover, there was strong evidence that the phenyl rings of the two series interact differently with the hydrophobic domain of the receptor site, with the increased flexibility of the benzylamino series enabling these compounds to bind with greater affinity.

Previous studies with phenylurea inhibitors indicated an adverse effect on activity of *ortho*-substitution in the phenyl ring (*20*). In the case of the benzylamino-2-cyanoacrylates, activity can be reduced almost 1000-fold when an 2-chloro substituent replaces 4-chloro (compare **10** and **11**). The *ortho*-substituent must exert sufficient steric influence to prevent the phenyl ring achieving the conformation required for optimal interaction with the binding site.

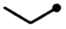
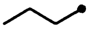
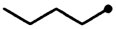
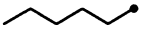
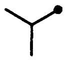
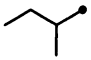
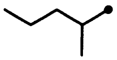
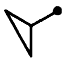
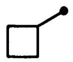
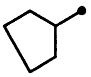
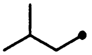
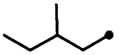
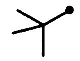
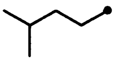
The importance of steric interactions within the hydrophobic domain occupied by R^1 was reinforced by differences in potency observed between the enantiomers **13** and **14** (*15*). The S(+) isomer **13** is 200-fold more active than the corresponding R(-) isomer **14**. Thus, the topographical characteristics of the binding site discriminate between the different spatial orientation of the groups around the chiral center in **13** and **14** (*15*).

The β-substituent, R^2. In 2-cyanoacrylates **3** where R^1 was alkyl-, aryl- and aralkyl-amino, inhibition of photosynthetic electron transport was enhanced by alkyl substitution at the β-carbon. With straight-chain alkyl groups, activity reached a maximum when a β-ethyl substituent was present in the molecule (*13,14*). Further increasing the alkyl chain length decreased activity indicating that the R^2 region of the receptor site also has strict spatial requirements. The data presented in Table II clearly indicate that steric arrangement of the carbon atoms is a primary determinant of binding affinity. Maximum activity appears to be associated with a branch at the α-carbon. The compound **15** (R^2=*iso*propyl) exhibited highest potency and is 50 times more active than the corresponding *n*-propyl isomer. Similar differences are associated with the spatial arrangement when R^2 is a four carbon unit, with *sec*butyl being 1000 and 450 times more potent than *n*-butyl and *iso*butyl respectively. Cyclic analogues were less potent than their α-branched isomers though the loss in activity was less than with other arrangements of atoms (Table II). A similar situation occurred when the β-substituent was a five-carbon unit. The most active isomer **15** (R^2=2-methylbutyl) was ten-fold less active than the lower homologue **15** (R^2=*sec*-butyl) but much more active than any other steric arrangement containing five carbon atoms. Increasing the number of carbon atoms of the β-substituent obviously increased the lipophilicity of the molecule as a whole and this factor may well have obscured the exact nature of the steric constraints of the binding site. However, a relatively small

Table II. Comparison of Hill Inhibition Activities of Compounds of General Formula (15) containing Straight and Branched-chain Alkyl Substituents



(15)

	2—carbon unit	3—carbon unit	4—carbon unit	5—carbon unit
R^2				
pI_{50}	7·20	6·50	5·00	3·80
R^2				
pI_{50}		8·20	7·95	6·95
R^2				
pI_{50}		7·10	6·95	5·95
R^2				
pI_{50}			5·30	4·60
R^2				
pI_{50}			*3·80	3·80

Compound **15** is the *E*-isomer: this may account for the low pI_{50} (*18*)

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

substituent branched at the α-carbon appeared to be the most favorable for high affinity binding.

The ester substituent, R^3. The nature of the ester substituent can also markedly influence Hill activity, though the interactions in this region of the binding domain are less well understood than the primarily lipophilic domain occupied by R^1 and R^2.

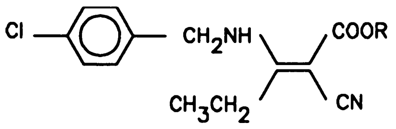
Simple alkyl esters were moderately active (compounds **17**, **18**, **20** and **22**, Table III). When a methoxy group was added to the ethyl ester (compound **19**), significantly enhanced activity is observed. The pI_{50} value reached a maximum when the R^3 substituent was ethoxyethyl (compound **10**), with an increase of 400-fold in potency over the simple ethyl ester **18**. It is likely that the effect of the ether oxygen atom on activity is related to its polar character and to its ability to interact with hydrogen bond donor groups of water or peptide molecules. The position of the ether oxygen atom in the sidechain appears critical since addition of a methoxy group did not significantly increase the activity of the propyl ester (compare compounds **20** and **21**). Moreover, a large decrease in potency was evident when the ether oxygen atom was located one atom further along the ester sidechain (compare compounds **21** and **10**). It was somewhat surprising, therefore, that addition of a methoxy group to the *n*-butyl ester enhanced activity ten-fold (compounds **22** and **23**). It is possible that the methoxybutyl group has sufficient flexibility to allow its ether oxygen atom to achieve some interaction at the same location as the oxygen atoms in the shorter sidechains of compounds **10** and **19**.

There is evidence for some steric constraint in the binding domain of the ester function. Inclusion of a branch at the α-carbon of the ester sidechain results in a dramatic decrease in activity (compare compound **24** with **10** and **19**). A similar situation pertains when the R^3 moeity includes a cyclic ether. Where branching occurs at the α-carbon (compound **26**), the inhibitor is 100-fold less active than **25** where a methylene group is interposed between the ester and the furfuryl ring. This difference occurs despite the ether oxygen being two carbon atoms removed from the ester function in both cases. Obviously, steric crowding at the α-carbon of the ester sidechain is inimical to optimal binding affinity.

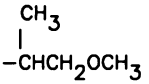
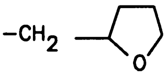
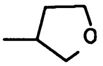
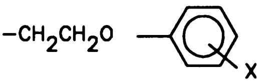
The phenoxyethyl esters (e.g. compounds **27-30**) were moderate to highly potent inhibitors depending on the nature and position of the phenyl substituent. QSAR analysis of the effect of substitution of the phenyl ring in this series presented quite a different picture from the simple dependence on lipophilicity observed with R^1. A series of *meta*-substituted phenoxyethyl esters was analyzed and pI_{50} was found to depend only on the size of the substituent with, in general, a bulky substituent causing loss of activity. A comparison between the activity of compounds substituted in different positions in the phenyl ring (e.g. compounds **28-30**) revealed that *ortho* and *meta* substituents conferred almost equal potency irrespective of the nature of the substituent, while *para*- substituted derivatives were generally over 100-times weaker (*19*). It is unlikely that phenyl ether sidechains interact with the binding domain in the same way as the alkyl ethers, particularly if interaction involves hydrogen bonding with water or peptide molecules. Phenyl ethers form weaker hydrogen bonds than alkyl ethers and, moreover, *ortho*-substitution does not diminish activity in the phenoxyethyl ester series. Thus, it is possible that the phenoxy esters bind to the receptor with a different orientation from that of the alkoxy esters. The region of the site occupied by the phenyl ring in the phenoxyethyl ester

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

Table III. Activity of Compounds of General Formula (16) as Inhibitors of the Hill Reaction



(16)

Compound No	R	pI_{50}
17	$-CH_3$	5·8
18	$-CH_2CH_3$	6·1
19	$-CH_2CH_2OCH_3$	7·2
10	$-CH_2CH_2OCH_2CH_3$	8·7
20	$-CH_2CH_2CH_3$	5·9
21	$-CH_2CH_2CH_2OCH_3$	6·1
22	$-CH_2CH_2CH_2CH_3$	5·6
23	$-CH_2CH_2CH_2CH_2OCH_3$	6·7
24	 $-\overset{CH_3}{\overset{\vert}{C}}HCH_2OCH_3$	5·5
25		7·2
26		5·2
		
27	X = H	8·0
28	X = 2Cl	8·0
29	X = 3Cl	8·2
30	X = 4Cl	5·8

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

series must be subject to stringent spatial constraints since *para*-substitution (e.g. compound **30**) is particularly detrimental to inhibitor activity.

Because the measured pI_{50} in 2-cyanoacrylates **3** appears to be the result of multiple interaction of the substituent groups with the binding site, it should be possible to increase the activity of compounds in Table III by optimizing the functionality on the left-hand side of the molecule. Thus, a more favorable β-substituent such as *iso*propyl (see Table II) in place of the β-ethyl substituent in **19** (Table III) resulted in a molecule with a pI_{50} of 8.2, i.e., a ten-fold increase in activity.

Herbicidal Activity.

2-Cyanoacrylates exhibit phytotoxic symptoms typical of the PSII herbicides. The compounds are only effective post-emergence and the herbicidal action is slow with plant death normally requiring three weeks from application under glasshouse conditions.

Active compounds showed a uniform selectivity pattern with marked specificity towards dicotyledonous species and a good margin of safety on most cereal crop species, e.g., wheat, oats, barley, maize and rice. Sensitive species include mustard (*Chenopodium alba*), pigweed (*Portulaca oleracea*), *Brassica* species, capeweed (*Arcotheca calendula*), wild radish (*Rashanus raphanistrum*), *Amaranthus* species, linseed (*Linum usitatissimum*), sugar beet (*Beta vulgaris*) and lupins (*Lupinus albus*).

The herbicidal activity of 2-cyanoacrylates of general formula **3** correlates reasonably well with pI_{50} data when sensitive species are considered. Compounds with pI_{50} values below 6 had little or no herbicidal activity at the highest rate assayed in the glasshouse (usually 8 kg/ha). In contrast, the commercial herbicide, atrazine, has a pI_{50} of 5.8 under the same Hill assay conditions.

Table IV gives an indication of the selectivity and levels of activity of representative 2-cyanoacrylates under glasshouse conditions. Of particular interest is the difference in activity shown by the optical pair, compounds **13** and **14**. Compound **14** is inactive at 8 kg/ha on all species tested and is at least 64 times less active than its enantiomer **13** on the most sensitive species, linseed and mustard. This level of discrimination is a reasonably accurate reflection of the difference in intrinsic activity of the two molecules in inhibiting photosynthetic electron transport. Correlation between inhibition of the Hill reaction and whole plant phytotoxicity breaks down in the series incorporating a phenoxyethyl ester (e.g., compounds **27-30**). Although compound **27** and analogues with 2- and 3-substituents in the phenyl ring are potent inhibitors they have little or no effect in the glasshouse at the highest rates tested.

Conclusions.

2-Cyanoacrylates **3** are highly potent inhibitors of photosynthetic electron transport with selective post-emergence herbicidal activity. The binding characteristics of the R^1 and R^2 groups of structure **3** suggests that these groups interact with a large lipophilic region. Earlier quantitative structure activity studies with PSII inhibitors (*21,22,23*) revealed the prime importance of lipophilicity in Hill inhibitory activity. In some series of PSII inhibitors, electronic effects play a significant role in the biological action (e.g. *24,25*), while steric effects were also noted in certain instances (*20,21,23*). In the cyanoacrylate

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

Table IV. Post-Emergence Herbicidal Activity of Representative 2-Cyanoacrylates (3) against Selected Species

Compound	*Peas*	*Mustard*	*Barley*	*Maize*	*Linseed*	*Ryegrass*
5	0	3	0	0	2	0
10	2	5	0	0	2	0
12	0	3	0	0	4	0
13	0	5	0	0	5	0
14	0	0	0	0	0	0
27	0	0	0	0	0	0

Compounds applied to 2-week-old seedlings in acetone/H_2O with 0.02% Tween 20.

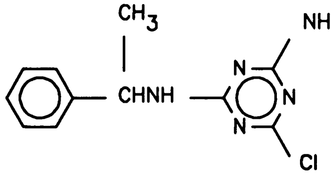
Activity Ratings: 0 = No activity at 2 kg/ha
1 = >80% plants killed at 2 kg/ha
2 = >80% plants killed at 1 kg/ha
3 = >80% plants killed at 0.5 kg/ha
4 = >80% plants killed at 0.25 kg/ha
5 = >80% plants killed at 0.125 kg/ha

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

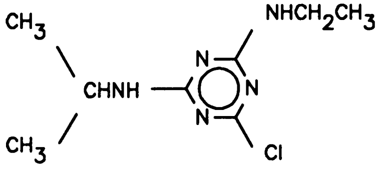
series, electronic effects were unimportant but steric requirements were clearly evident and the spatial arrangement of groups in the molecule which provided a "best fit" for the receptor could be inferred (*13,14*).

Manipulation of the ester substituent R^3 revealed interactions different from those observed on the left-hand side of the molecule. Lipophilicity was unimportant and studies with sidechains containing an ether oxygen atom suggested the presence of a specifically-located hydrophilic pocket or water interface which could contribute to binding. Moreover, discontinuities in this region of the binding domain were also evident making steric factors important.

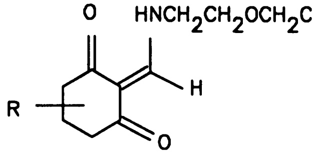
The delineation of favorable sub-structures for R^1,R^2 and R^3 has enabled a wide range of PSII inhibitors based on the cyanoacrylate core structure to be prepared. Moreover, certain of these structural features have been used to good effect in increasing activity in other PSII inhibitor series. For example, ethoxyethyl and α-methybenzyl substituents incorporated into the triazine structure **31** gave a significant increase in activity over the N-ethyl-N-*iso*propyltriazine (atrazine) **32** (*26*). Similarly ethoxyethylamino substituents were incorporated into a series of 1,3-cyclohexanedione derivatives (compounds of structure **33**) which are potent PSII inhibitors (*27*). Two new classes of heterocyclic PSII inhibitors incorporate substituted benzyl groups, favorable lipophilic substituents common to the cyanoacrylate series (e.g. compounds **34** and **35**) (*28*).



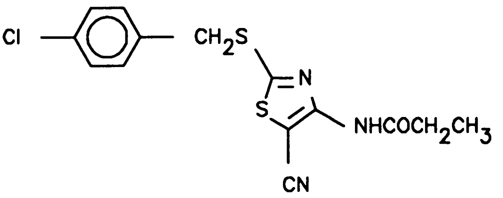
31



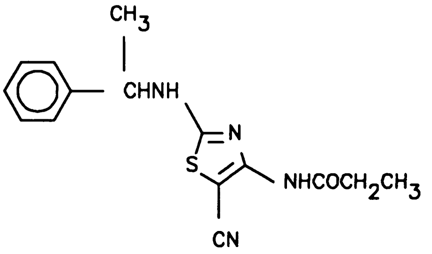
32



33



34



35

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

Structure-activity and QSAR studies of the 2-cyanoacrylates and other PSII inhibitors combined with photo-affinity labeling experiments and the effects of D1 protein mutations on inhibitor binding has provided considerable information concerning the topography of the inhibitor binding site. Computer-based molecular modeling has been used to construct a 3-dimensional structure of the binding niche (*26,29*) which has enabled detailed study of possible interactions between inhibitor molecules and the protein. Identification of crucial binding regions and the types of interaction associated with high affinity binding should enable the design of novel, highly potent inhibitors as potential PSII herbicides.

Acknowledgments.

The authors wish to thank Dr John Phillips for his continued interest in this work and Barbara Cronin, Kate Edgerley and Wendy Banham and the late Barbara Rattigan for expert technical assistance.

Literature Cited.

1. Fedtke, C. *Biochemistry and Physiology of Herbicide Action*; Springer-Verlag: Berlin, 1982; p19-85.
2. Vermass, W.F.J.; Renger, G.; Arntzen, C.J. *Z. Naturforsch.*, **1984,** *39c,* 368-373.
3. Pfister, K.; Arntzen, C.J. *Z. Naturforsch.* **1979,** *34c,* 996-
4. Trebst, A.; Draber, W. In *Advances in Pesticide Science, Pt.2*; Geissbuhler, H., Ed.; Pergamon: Oxford, 1979; p 223.
5. Draber, W. *Z. Naturforsch.* **1987,** *42c,* 713-717.
6. Scheuermann, H.; Fischer, A., S. African Patent 68 05 817, 1969; *Chem. Abstr.* **1970**, 72, 20790.
7. Scheuermann, H.; Fischer, A., French Patent 1 579 902, 1969; *Chem. Abstr.* **1970**, 72, 121209.
8. Fischer, A., German Patent 1 950 601, 1971; *Chem. Abstr.* **1971**, 75, 47729.
9. Huppatz, J.L.; Phillips, J.N.; Rattigan, B.M. *Agric. Biol. Chem.* **1981,** *45,* 2769-2773.
10. Michaely, W.J.; Chin, H.M.; Curtis, J.K.; Knudsen, C.G. In *Synthesis and Chemistry of Agrochemicals*; Baker, D.R.; Fenyes, J.G.; Moberg, W.K.; Cross, B., Eds.; ACS Symposium Series 355; American Chemical Society: Washington, DC, 1987; pp 113-121.
11. Phillips, J.N.; Huppatz, J.L, *Agric. Biol. Chem.* **1984,** *48,* 51-54.
12. Phillips, J.N.; Huppatz, J.L. *Agric. Biol. Chem.* **1984,** *48,* 55-58.
13. Huppatz, J.L.; Phillips, J.N. *Z. Naturforsch.* **1984,** *39c,* 617-622.
14. Huppatz, J.L.; Phillips, J.N. *Z. Naturforsch.* **1987,** *42c,* 679-683.
15. Huppatz, J.L.; Phillips, J.N *Z. Naturforsch.* **1987,** *42c,* 684-689.
16. Huppatz, J.L.; Phillips, J.N. *Z. Naturforsch.* **1987,** *42c,* 674-678.
17. Rathke, M.W.; Cowan, P.J. *J. Org. Chem.* **1985,** *50,* 2622-2627.
18. McFadden, H.G.; Craig, D.C.; Huppatz, J.L.; Phillips, J.N. *Z. Naturforsch* . **1991,** *46c,* 93-98.
19. Huppatz, J.L.; McFadden, H.G.; McCaffery, L.F. *Z. Naturforsch.* **1990,** *45c,* 336-342.
20. Camilleri, P.; Bowyer, J.R.; Gilkesson, T.; Odell, B.; Weaver, R.C. *J. Agric. Food Chem.* **1987,** *35,* 479-483.
21. Kakkis, E.; Palmire, V.C.; Strong, C.D.; Bertsch, W.; Hansch, C.; Schirmer, U. *J. Agric. Food Chem.*, **1984,** *32,* 133-144, and references cited therein.
22. Takemoto, I.; Yoshida, R.; Sumida, S.; Kamoshita, K. *J. Pesticide Sci.*, **1984,** *9,* 517-521.
23. Mitsutake, K.; Iwamura, H.; Shimizu, R.; Fujita, T. *J. Agric. Food Chem.*, **1986,** *34,* 725-735.

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

24. Camilleri, P.; Barker, M.D.; Kerr, M.W.; Whitehouse, M.K.; Bowyer, J.R.; Lewis, R.J. *J. Agric. Food Chem.*, **1989**, *37*, 1509-1513.
25. Camilleri, P.; Astles, D.P.; Kerr, M.W.; Spencer, J.E. *J. Agric. Food Chem.*, **1990**, *38*, 1601-1603.
26. Tietjen, K.G.; Kluth,J.F.; Andree, R.; Haug, M.; Lindig, M.; Müller, K.H.; Wroblowsky, H.J.; Trebst, A. *Pestic. Sci.*, **1991**, *31*, 65-72.
27. Yoshida, S. *Z. Naturforsch.* **1990**, *45c*, 329-335, and references cited therein.
28. Kluth, J.F.; Tietjen, K.G.; Andree, R.; Ewald, G.; Oettimeier, W.; Trebst, A. *Pestic. Sci.* **1990**, *30*, 424-427.
29. Bowyer, J.; Hilton, M.; Whitelegge, J.; Jewess, P,; Camilleri, P.; Crofts, A.; Robinson, H. *Z. Naturforsch.* **1990**, *45c*, 379-387.

RECEIVED June 26, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch018

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

Chapter 19

Synthesis and Gametocidal Activity of 1-Aryl-5-(aminocarbonyl)-1*H*-pyrazole-4-carboxylic Acids

Michael P. Lynch[1], Stephen A. Ackmann[1], Dale R. Heim[1], George E. Davis[1], Michael A. Staszak[2], James R. Beck[2], Edward E. Tschabold[2], and Fred L. Wright[2]

[1]Discovery Research, DowElanco Research Laboratories, 2001 West Main Street, Greenfield, IN 46140
[2]Lilly Research Laboratories, Eli Lilly and Company, Lilly Industrial Center, Indianapolis, IN 46285

A series of 1-aryl-5-(aminocarbonyl)-1H-pyrazole-4-carboxylic acids were serendipitously discovered to be chemical hybridizing agents. Different synthetic routes were developed for the active analogs depending on whether an electron withdrawing group or electron donating group was present on the phenyl ring. Development of the "second generation gametocides" produced analogs which were 5-6 times more active than the original lead.

Hybridization of plants has long been known to be a desirable means of increasing the physical and productive qualities of crops. Seed hybrids are available on a commercial scale for only a few crops: corn, sorghum and some vegetables. For many years breeders have utilized a number of techniques to create a mass hybridization system for a variety of crops (*1*). The key to hybridization is achieving male sterility. Over the years a number of techniques have been utilized to achieve male sterility. The first method developed was the mechanical or manual method of sterilization. This method simply involved the removal of the plants' anthers. Depending on the species this method can be extremely difficult. Since in most crops the anthers and pistils are in close proximity of each other, manual removal can be extremely time consuming and costly. More recently, breeders have used such techniques as cytoplasmic male sterilization and a newer technique called nuclear male sterilization. Of course, a number of companies have been involved in the synthesis and development of chemical hybridizing agents (*2-9*).

In the early 1980's the Plant Science Discovery Group initiated a screen for chemical hybridizing agents. The target crop was spring wheat since it could be grown to flowering and seed set under greenhouse conditions. The pyrazole carboxamide chemical hybridizing agents **4a** were discovered during an investigation of pyrazole derivatives which had herbicidal properties (Figure 1). Treatment of the common intermediate cyano ester **1** with methylamine led to **2**, which exhibited preemergent control of *Alopecurus* in European cereals (*10,11*). This research eventually led to the synthesis of **3** which was evaluated as a pre- and postemergent herbicide in cereals and corn (*10,12*). Saponification of the common intermediate **1a** with potassium hydroxide resulted in the discovery of the gametocides (*13*).

0097–6156/92/0504–0200$06.00/0

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

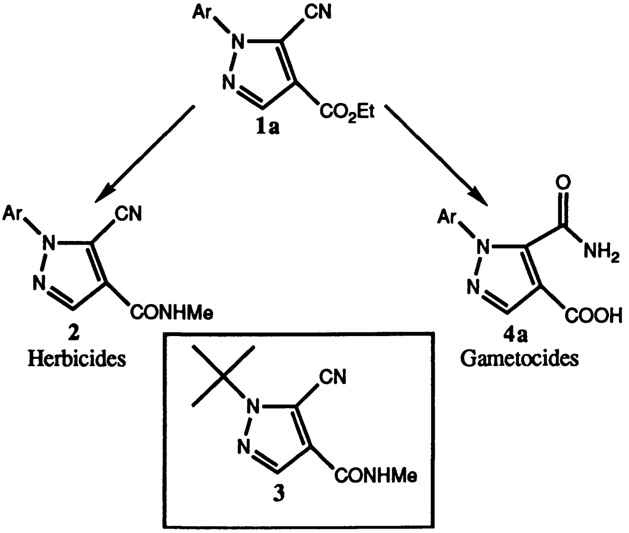

Ar
CN
N
N
CO2Et
1a
Ar
CN
CONHMe
2
Herbicides
Ar
O
NH2
COOH
4a
Gametocides
CN
CONHMe
3

Figure 1. Synthesis of pyrazole herbicides and gametocides from intermediate 1.

Method of Preparation

The discovery of the gametocides was a result of the synthesis of a series of 1-aryl-5-chloro-1H-pyrazole-4-carboxamides (Figure 2). The synthesis was initiated by reacting phenylhydrazine with ethyl (ethoxymethylene)cyanoacetate to produce the pyrazole amino ester **5**. Treatment of **5** with excess nitrosyl chloride in chloroform at room temperature gave the chloro ester **6**. Nitrosyl chloride is no longer commercially available, but can be synthesized in the laboratory (*14*). The chloro ester **6** was saponified with potassium hydroxide to produce the carboxylic acid **7** in quantitative yield. Finally, treatment of **7** with carbonyldiimidazole (CDI) and aqueous methylamine in DMF produced the pyrazole carboxamide **8**, which was found to exhibit preemergent herbicidal activity at 4 lb/acre against crabgrass, pigweed, foxtail and velvetleaf.

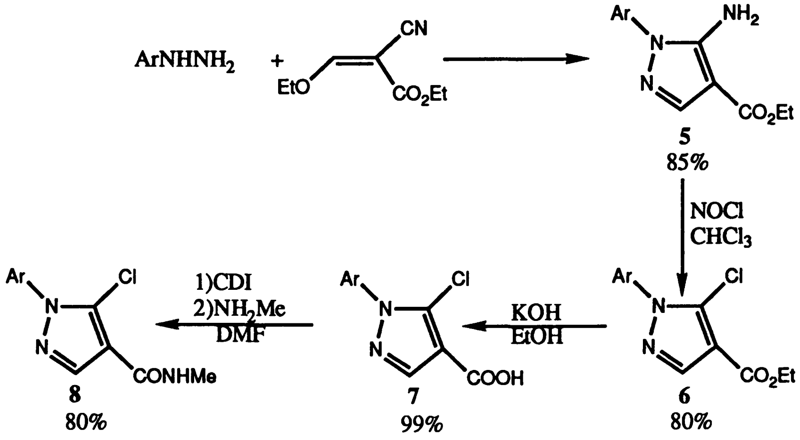

ArNHNH2
+
CN
EtO
CO2Et
Ar
NH2
N
N
CO2Et
5
85%
NOCl
CHCl3
Ar
Cl
CO2Et
6
80%
KOH
EtOH
Ar
Cl
COOH
7
99%
1)CDI
2)NH2Me
DMF
Ar
Cl
CONHMe
8
80%

Figure 2. Synthesis of 5-chloro-1-aryl-N-methyl-1H-pyrazole-4-carboxamides.

This research led to the development of novel pyrazole chemistry which provided a new series of herbicidally active compounds. As depicted in Figure 3 a number of herbicidal 1-aryl-5-chloro-1H-pyrazole-4-carbonitriles **10** were prepared (*15*). A cyano group was introduced in the 5-position of the pyrazole ring via a nucleophilic displacement reaction, using sodium cyanide in DMF, but the resultant bis cyano pyrazoles **11** lacked herbicidal activity at 8 lbs/acre.

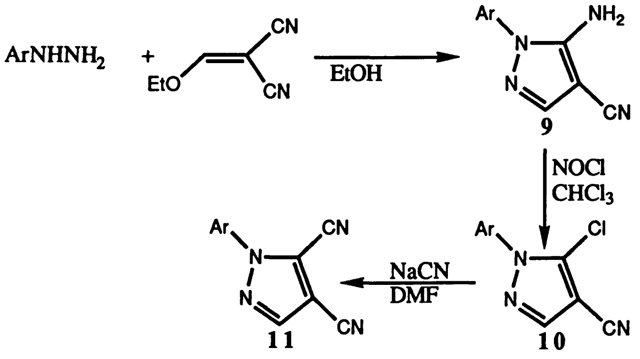


Figure 3. Synthesis of 1-aryl-1H-pyrazole-4,5-dicarbonitriles.

When **6** was treated with two equivalents of sodium cyanide in DMF and heated to 100°C for two hours the 5-cyano pyrazole ester **1a** was produced. Saponification of **1a** produced the cyano acid **12**. Finally, treatment of **12** with CDI and aqueous methylamine produced the pyrazole cyano carboxamide **2** (Figure 4). It was also discovered that a direct aminolysis of **1a** using aqueous methylamine in methanol could produce **2** in 90% yield. Compound **2** was active at 0.5 lb/acre in the greenhouse, and this derivative was pursued as a preemergent cereal herbicide (*10,16*).

The key step in the reaction sequence in Figure 4 was the saponification of **1a** to the cyano acid **12**. Reaction conditions had to be monitored carefully because there was the possibility that the nitrile could be hydrolyzed. The cyano ester **1a** was taken up in ethanol, potassium hydroxide was added and the solution was heated on the steam bath for five minutes. The solution was then cooled, poured over ice water and acidified with concentrated hydrochloric acid to produce **12a**. However, when a solution of **1b** and potassium hydroxide in ethanol was heated for an hour on the steam bath the nitrile was indeed hydrolyzed. Figure 5 shows the products that were formed in these two reactions.

The first analog synthesized in the serendipitous discovery of the pyrazole amide acids was the 3-chlorophenyl analog **4b**. The initial greenhouse testing indicated that this analog inhibited anther formation. A structure activity relationship (SAR) was initiated and three parameters were investigated. The first parameter studied was the phenyl ring monosubstitution (Figure 6). The 3-Cl and 3-Me derivatives were found to be the most active, with the 3-Me being slightly more active. Substitution in the ortho position resulted in inactivity, and substitution in the para position resulted in reduced activity.

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

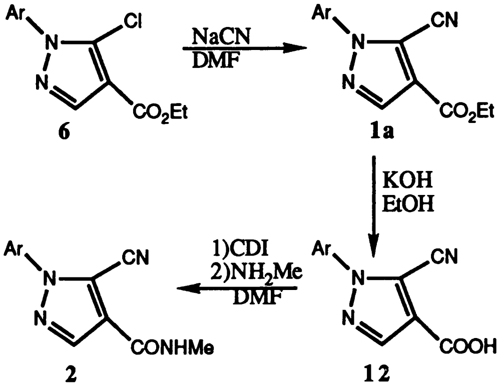

Ar
N
N
Cl
CO2Et
6
NaCN
DMF
Ar
CN
CO2Et
1a
KOH
EtOH
Ar
CN
COOH
12
1)CDI
2)NH2Me
DMF
Ar
CN
CONHMe
2

Figure 4. Synthesis of 5-cyano-1-aryl-N-methyl-1H-pyrazole-4-carboxamides.

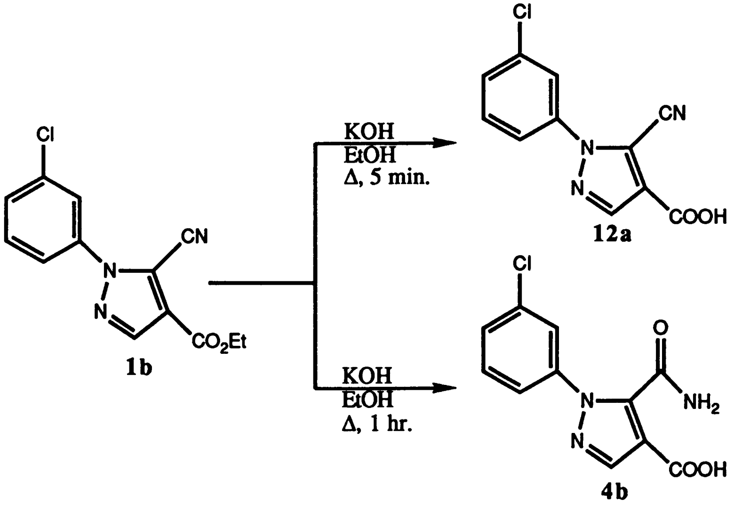
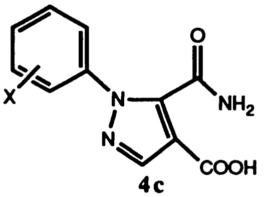

Cl
CN
N
N
CO2Et
1b
KOH
EtOH
Δ, 5 min.
Cl
CN
COOH
12a
KOH
EtOH
Δ, 1 hr.
Cl
O
NH2
COOH
4b

Figure 5. Treatment of the pyrazole cyano ester with potassium hydroxide under various refluxing conditions.



4c

X		
H	2,3-diCl	3,4-diCl
3-Cl	3-CF_3	4-CF_3
4-Cl	3-OMe	4-OCF_3
2-Cl	4-OMe	3-OCF_2CHF_2
2-Br	3-Me	4-$OCHF_2$
3-Br	4-Me	4-OCF_2CHF_2
4-Br	3,4-diMe	3-F
3-Cl,4-Me	4-F	3-Et
2,4-diCl	2-CF_3,4-Cl	

Figure 6. Phenyl ring substituents in the pyrazole amide acid series.

The next parameter investigated was the substitution at the carboxamide position. A new synthetic scheme was developed in order to achieve substitution at the carboxamide nitrogen (Figure 7). The amide acid **4b** was hydrolyzed with 48% hydrobromic acid to give the corresponding bis acid **13**. Treatment of the bis acid **13** with methanolic hydrogen chloride gave the bis methyl ester **14**. Treatment of this bis ester with hydroxide ion under mild conditions selectively yielded the half acid ester **15** (*17*). Treatment of the acid ester **15** with CDI followed by the appropriate amine resulted in the production of the amide ester **16**. Finally, treatment with sodium hydroxide in methanol produced the amide acid **17** (Figure 8). All analogs except for the primary carboxamide were inactive.

The third parameter investigated was alteration at the carboxylate functionality. The esters and salts **18** were prepared using standard reaction conditions (Figure 9) (*11*). The rationale for preparing the long chain aliphatic esters and Kemamine Salts was to enhance the lipophilicity of these analogs and hopefully have better penetration in the plant. Whole plant data (not listed) indicated that all analogs were inactive.

Finally, analogs isomeric with **4c** which had the acid and amide functionalities reversed were investigated. Reaction of **4c** with CDI produced the imide **19** which ring opened to give **20**, and all analogs were found to be inactive (Figure 10).

Kilogram quantity samples of the 3-Cl and 3-Me derivatives were required for field experiments. However, upon scale-up, a major problem developed with the synthesis of the 3-methylphenyl analog of **4c**. Treatment of the amino ester **5a** with nitrosyl chloride in chloroform resulted in the formation of significant amounts (30-40%) of the desamino ester **21** in addition to the expected chloro ester **6a** (Figure 11).

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

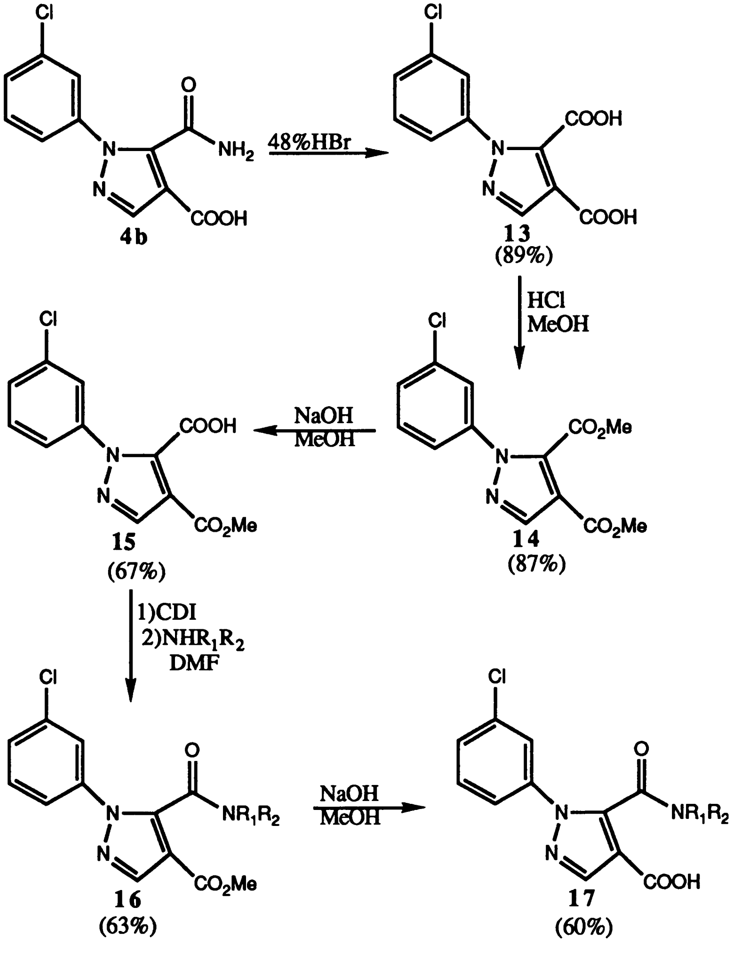
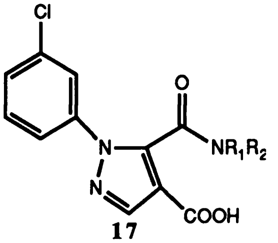

Cl
O
NH2
COOH
4b
48%HBr
COOH
COOH
13
(89%)
HCl
MeOH
CO2Me
CO2Me
14
(87%)
NaOH
MeOH
COOH
CO2Me
15
(67%)
1)CDI
2)NHR1R2
DMF
NR1R2
CO2Me
16
(63%)
NaOH
MeOH
NR1R2
COOH
17
(60%)

Figure 7. Synthesis of the pyrazole N-substituted carboxamide acids.

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

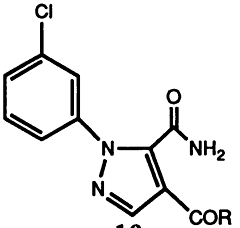
Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019



17

R_1	R_2
H	H
H	Me
Me	Me
H	Et
H	isoPr
H	CycloPr
H	CycloHex
H	Allyl
H	Ph

Figure 8. 3-Chlorophenyl-4-carboxylic acid-1H-pyrazole-5-carboxamides.



18

R	
OMe	OEt
OisoPr	OCH_2Ph
$O(CH_2)_3Me$	$O(CH_2)_5Me$
$O(CH_2)_7Me$	$O(CH_2)_9Me$
OAllyl	O^-Na^+
O^-K^+	Kemamine Salts

Figure 9. Functionalization at the 4-position of the pyrazole ring.

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

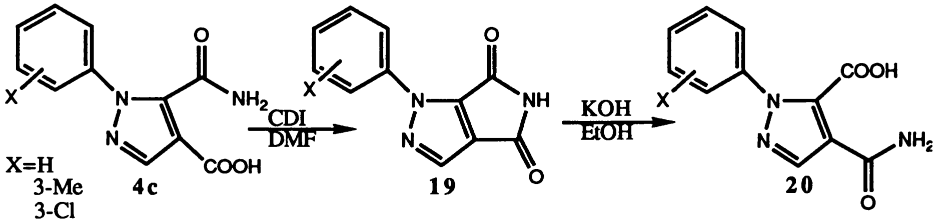

O
NH2
N
N
X
COOH
X=H
3-Me
3-Cl
4c
CDI
DMF
X
O
NH
O
19
KOH
EtOH
X
COOH
NH2
O
20

Figure 10. Preparation of the isomeric form of the pyrazole acid amide.

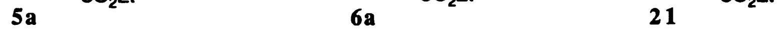

Me
NH2
N
N
CO2Et
5a
NOCl
CHCl3
Me
Cl
CO2Et
6a
+
Me
CO2Et
21

Figure 11. Synthesis of the chloro ester **6a** and the desamino ester **21**.

Alternatively, the field trial sample was prepared by the route illustrated in Figure 12. The pyrazole amino ester **5a** was converted to the methylthio ester **22** utilizing nonaqueous diazotization conditions. The yield of **22** was increased to 85% by carefully controlling the rate of addition of t-butyl nitrite to a solution of **5a** and dimethyl disulfide in chloroform. The yield of desamino product **21** in this case was only 1-2%. Oxidation of **22** with hydrogen peroxide in acetic acid produced the methyl sulfone **23** in 90% yield. Treatment of **23** with sodium cyanide (2.2 equivalents) in DMF at 80°C for 35 minutes yielded the cyano ester **1b** in 96% yield. Finally, saponification of **1c** gave the desired product **4c**.

As a consequence of the synthetic investigations a number of conclusions have been reached: 1) the nitrosyl chloride process was found to be superior with electron-withdrawing groups on the aryl ring, and the methylthio route was found to be superior with electron-donating groups present, 2) the nitrosyl chloride process gives higher yields in the presence of hydrogen chloride and 3) cyanide displacement of methylsulfonyl is faster than chloro (*11*).

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

Biological Testing

In the field results with **4c** (X=3-Me) (Table 1) each multiple treatment resulted in at least 95% male sterility. Seed set compared to untreated controls ranged from 61% at the lowest treatment of 2.24 Kg ha^{-1} to 1% at the highest rate of 33.6 Kg ha^{-1}. As rates increased, total seed set decreased.

The 3-Me analog of **4c** applied in single treatments also produced high levels of sterility, although the efficacy depended on treatment timing. When applied at the second date, 3.36 Kg ha^{-1} produced 98% sterility. The 11.2 Kg ha^{-1} rate at either of the first two treatment dates produced plots that were totally sterile. At each treatment date, the main shoots of several plants were harvested and were dissected to determine the size of the flowering spike. The most effective application was when the average main shoot spike was about 5 mm long.

High application rate of **4c** (X=3-Me) prevented anther development (Figure 13). Lower doses resulted in progressively less inhibition, but still caused an abnormal morphology characterized by smaller, twisted and more intensely pigmented locules (*19*). No biochemical mechanism has been suggested.

Recent structure activity studies on bis phenyl substitution resulted in the synthesis of the "second generation gametocides", namely **4c** (X=3,5-diMe and X=3,5-diCl) which were 5-6 times more active than the original lead compound **4c** (X=3-Me) (no data shown). Other multiply substituted analogs prepared during the second phase of synthesis were all found to be inactive (Figure 14) (*20*).

Summary

The 1-(3-chlorophenyl) and 1-(3-methylphenyl)-5-(aminocarbonyl)-1H-pyrazole-4-carboxylic acids **4b** and **4c** are a new class of chemical hybridizing agents. The large scale synthesis of these analogs was achieved by two different routes depending on whether an electron donating group or electron withdrawing group was present on the phenyl ring. A split foliar application of the active analogs appeared to provide the best percentage of sterility. The "second generation gametocides" provided an enhanced sterilizing capacity and were 5-6 times more active than the original lead in greenhouse testing.

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

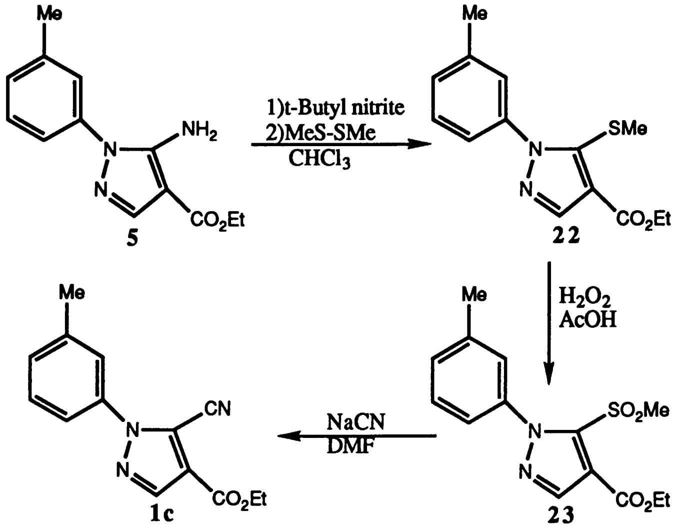

Me
NH2
N
N
CO2Et
5
1)t-Butyl nitrite
2)MeS-SMe
CHCl3
Me
SMe
N
N
CO2Et
22
H2O2
AcOH
Me
SO2Me
N
N
CO2Et
23
NaCN
DMF
Me
CN
N
N
CO2Et
1c

Figure 12. Synthesis of the pyrazole cyano ester **1c** utilizing methylthio chemistry.

Table 1 Male sterilizing activity of **4c** (X=3-Me) on Caldwell Wheat †

Treatment regime	Compound Rate Kg ha^{-1}		
	2.2	3.4	11.2
	% Sterility		
1	20.0	91.0	100.0
2	55.1	99.8	100.0
3	13.9	70.3	94.3
4	98.4	100.0	100.0
5	98.3	99.9	100.0

†Foliar applications were made on three different dates. Experimental plots for Regimes 1, 2 and 3 received single treatments on dates 1, 2 and 3, respectively. Regime 4 consisted of duplicate treatments to specified plots on dates 1 and 2, and the plots of Regime 5 received three similar applications, one on each treatment date. Treatment intervals in all cases were 7 days.

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

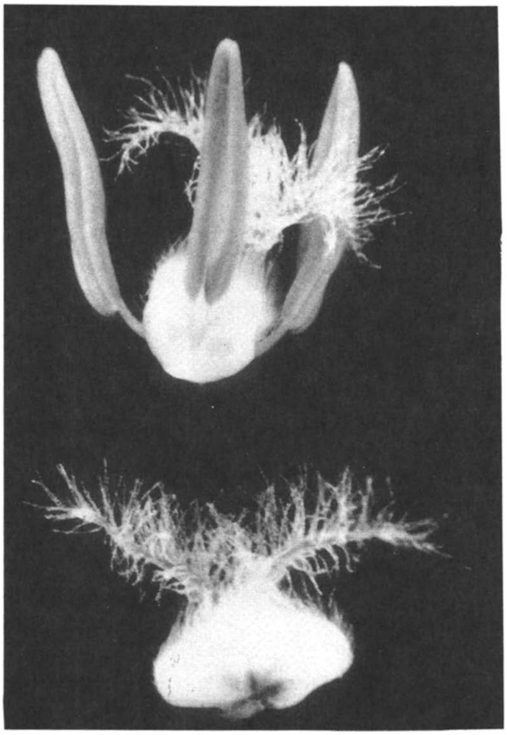
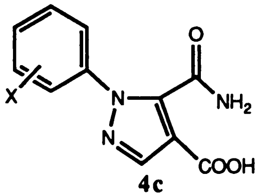


Figure 13. Excised florets from wheat heads of a control plot (top) and from a plot treated with 7.73 Kg ha^{-1} of the 3-methylphenyl analog **4c** with split foliar application. Reproduced with permission from ref. 19. Copyright 1988 Crop Science Society of America, Inc..



4c

X	
3,5-diMe	2,5-diCl
3,5-diCl	3,5-diCF$_3$
2,3,4,5-tetraCl	3,4,4-triCl
3,5-diF	3,4,5-triMe
2,4,5-triCl	

Figure 14. List of "second generation gametocides."

Literature Cited

1) Agrichemical Age, Oct. 1990, p.20.
2) Searle, R. J. G.; Day, J. A., U.S. Patent 4,249,936, 1981.
3) Searle, R. J. G.; Day, J. A., U.S. Patent 4,288,367, 1981.
4) Devlin, B. J. R., U.S. Patent 4,560,401,1986.
5) Fujimoto, T. T., U.S. Patent 4,661,145, 1987.
6) Carlson, G. R., U.S. Patent 4,714,492, 1988.
7) Labovitz, J. N.; Fang, L., U.S. Patent 4,729,782, 1988.
8) McDaniel, R. G., U.S. Patent 4,925,477, 1990.
9) Carlson, G. R., U.S. Patent 4,964,896, 1990.
10) Beck, J. R., U.S. Patent 4,589,905, 1986.; see also Chem. Abstr., **1985**,103.
11) Beck, J. R.; Lynch, M. P.; Wright, F. L., *J. Heterocyclic Chem.*, **1988**, *25*,555.
12) Michael P. Lynch, James R. Beck, Eddie V. P. Tao, James Akins, George Babbitt, John R. Rizzo, and T. William Waldrep, *Synthesis and Chemistry of Agrochemicals II*; Don R. Baker, Joseph G. Fenyes and William K. Mosberg, ACS Symposium Series No. 443; Washington D.C., 1991, pp. 144-157.
13) Beck, J. R.; Price, C. W., European Pat. Appl.: 177242, **1986**.
14) Ratcliffe, Charles, T.; Shreeve, Jean'ne, M., *Inorg. Syn.*, **1968**, *11*, 194.
15) Beck, J. R.; Lynch, M. P., U.S. Patent 4,563,210, 1986.; see also Chem. Abstr., 1986, 105, 42791.
16) Beck, J. R.; Gajewski, R. P.; Lynch, M. P.; Wright, F. L., *J. Heterocyclic Chem.*, **1987**, *24*, 267.
17) R. G. Jones and C. W. Whitehead, J. Org. Chem., **1955**, *20*, 1342.
18) James R. Beck, Stephen A. Ackmann, Michael A. Staszak and Fred L. Wright, *J. Heterocyclic Chem.*, **1988**, *25*, 955.
19) E. E. Tschabold, D. R. Heim, J. R. Beck, F. L. Wright, D. P. Rainey, N. H. Terando and J. F. Schwer, *Crop Science*, **1988**, *28* (4), 583.
20) Stephen A. Ackmann, James R. Beck and Fred L. Wright, U.S. Patent 4,801,326, 1988.

RECEIVED June 1, 1992

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch019

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

Chapter 20

Discovery, Isolation, and Structure Elucidation of a Family of Structurally Unique, Fermentation-Derived Tetracyclic Macrolides

Herbert A. Kirst[1], Karl H. Michel[1], Jon S. Mynderase[1], Eddie H. Chio[1], Raymond C. Yao[1], Walter M. Nakasukasa[1], LaVerne D. Boeck[1], John L. Occlowitz[1], Jonathon W. Paschal[1], Jack B. Deeter[1], and Gary D. Thompson[2]

[1]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285
[2]Discovery Research, DowElanco Research Laboratories, Greenfield, IN 46140

Screening of fermentation broths for mosquito larvicidal activity yielded an active culture denoted as A83543. Nine active, structurally-related factors were isolated and purified by extractive and chromatographic procedures. Their structures were elucidated by a combination of spectroscopic (NMR, MS, UV, IR) and X-ray crystallographic methods. Each factor possessed the core structure of a 5,6,5-*cis-anti-trans*-tricyclic ring system fused to a 12-membered lactone. In addition, an aminosugar (forosamine) and a neutral sugar (2,3,4-tri-O-methylrhamnose) were glycosidically linked to the tetracyclic framework. Absolute stereochemistry was established by comparing samples of forosamine obtained from acidic hydrolyses of A83543A and spiramycin. The novel tetracyclic structure of A83543 suggests that unique features are involved in its biosynthesis. The purified factors exhibited potent mosquito larvicidal activity, but lacked antibiotic activity.

After several decades of intense investigation, screening of fermentation broths still remains a viable method for discovery of structurally novel compounds possessing biological activity (*1, 2*). The ability of physicians to treat most infectious diseases is largely a result of the successful development of fermentation-derived antibiotics and their semi-synthetic derivatives. This approach is now being more extensively applied to discover compounds that exhibit activity in a wide variety of non-anti-infective applications in both human and veterinary medicine (*2 - 5*).

Among the numerous classes of known fermentation products, the class of macrolides (or, more broadly, macrocyclic lactones) has been especially prominent in both structural and biological diversity of its members (*6, 7*). The discovery of A83543 adds another novel, structurally

0097–6156/92/0504–0214$06.00/0

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

unique family of compounds to the rapidly growing class of macrocyclic lactones possessing non-antibiotic biological activity.

Screening of Culture Broths and Discovery of an Active Culture

The discovery of new insecticides is an important research objective because of the continuing development of resistance to existing insecticides and the desire for agents with less environmental and mammalian toxicity (*8, 9*). It is particularly desirable to discover new chemical classes of insecticides which operate by different modes of action and, consequently, lack cross-resistance with currently employed insecticides. In this respect, screening fermentation broths can offer unique advantages, since this approach can uncover completely novel structures unlike any that have previously been synthesized, or even conceived, by organic chemists. Recent examples of novel fermentation products which have revolutionized a thereapeutic area include avermectin (anthelmintic), cyclosporin and FK-506 (immunosuppressive), and mevinolin and compactin (cholesterol-lowering).

Many previous studies have demonstrated that insecticides can be successfully isolated from fermentation broths (*10 - 16*). Furthermore, fermentation products may be useful as starting materials for the preparation of semi-synthetic derivatives possessing improved insecticidal activity. One such recent example is the conversion of avermectin to MK-243, which improved the insecticidal activity against various species by several hundred-fold (*17 - 19*). Based on literature precedents such as these, a program of screening fermentation broths for novel compounds with insecticidal activity is warranted.

Development of a screen that is both relevant for the target activity and amenable to complex culture broths (*i.e.*, both sensitive and selective) is a key prerequisite for the discovery of fermentation products. Historically, inhibition of microbial growth around a disk on an agar plate was just such a highly selective and sensitive assay system which, for more than four decades, led to the discovery of the currently known multitude of antimicrobial compounds. Thus, both the choice and the development of a screen are critical issues which must be addressed and solved if a fermentation products discovery program is to succeed.

Mosquito larvicidal activity has been employed for many years as an indicator assay for other insecticidal activities (*20, 21*). More recent applications of this methodology have been found in screening culture broths or studying various fermentation-derived natural products (*22, 23*). In the course of our screening culture broths from the fermentation of random soil microorganisms, a broth was found that exhibited activity against larvae of the mosquito, *Aedes aegypti*. This activity was produced by a microorganism, designated as A83543, that had been isolated from a soil sample collected in the Virgin Islands. Subsequent taxonomic studies indicated that this organism was a new species within the rare genus *Saccharopolyspora*. It has now been classified as *Saccharopolyspora spinosa* (*24*). This genus has not yet been extensively explored with respect to its potential for the production of secondary metabolites during fermentation (*25*).

Isolation of the Active Components from A83543 Culture Broths

The active components within the A83543 complex were isolated from the fermentation broth and purified by a combination of extractive and chromatographic procedures. The broth was initially filtered with the use of a filter aid (Hyflo, 1%), and the separated biomass was washed with water. The biomass was then agitated with methanol for approximately one hour to release and dissolve the desired product. The mixture was filtered and the filtrate was concentrated and then extracted three times with equal volumes of diethyl ether. The combined ether extracts were concentrated and chromatographed (in portions) by reversed-phase HPLC on an "Autoprep" automated HPLC system (Rainin Instrument Co), using a Lobar RP-8 column (size B; E. M. Industries, Inc.) and UV detection of active fractions at 250 nm (ISCO-V4 absorbance detector). The column was eluted with a solvent mixture of methanol-acetonitrile-water (49:49:2), with a flow rate of 8 mL/min and a cycle time of 28 min. The appropriate fractions were automatically combined from each of twelve cycles through the Autoprep system to yield several pooled fractions which were examined by mosquito larvicidal assay and analytical HPLC.

The analytical chromatography system (LDC Gradient Master III with a Constametris III pump and Spectromonitor III UV detector) employed a reversed-phase column (Nova 4 μ C18, 8 x 100 mm, Waters Associates) which was eluted with acetonitrile-methanol-water (45:45:10) containing ammonium acetate (0.05%) at 4 mL/min and UV detection at 250 nm. The active fractions were appropriately combined according to the results from the mosquito larvicidal assays and HPLC profiles. These combined fractions were further purified on the Autoprep system, using a high resolution reversed-phase preparative column (8 μ C18, 2.14 x 25 cm, Rainin Dynamax). Elution with methanol-acetonitrile-water mixtures then yielded the purified factors A83543A, B, C, and D.

An alternative procedure was also developed for isolation of the A83543 compounds. The methanolic extract of the biomass was concentrated and then applied to HP-20 resin (Mitsubishi Chemical Industries) suspended in water. The resin mixture was stirred for 1 hr and then poured into a column, drained, and eluted with methanol-water (1:1, then 7:3). Elution with methanol subsequently yielded the desired material. After evaporation of solvent, the residue was dissolved in methanol-THF (4:1) and precipitated by addition to acetonitrile (10 volumes). The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in methanol and applied to a column of Sephadex LH-20 (5.5 x 90 cm, Pharmacia LKB Biotechnology, Inc.) packed in methanol. The desired products were eluted with methanol, and appropriate fractions were combined according to bioassay and analytical HPLC results and evaporated. The residue, dissolved in methanol, was applied to a preparative reversed-phase HPLC column (8 μ C18, 4.11 x 25

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

cm, Rainin Dynamax) which had been conditioned in methanol-acetonitrile-water (37.5:37.5:25). The column was eluted with a linear gradient of methanol-acetonitrile-water, running from 37.5:37.5:25 to 45:45:10. Fractions containing pure A83543A were combined, evaporated, dissolved in *t*-butanol, and lyophilized. Fractions containing A83543D were combined, concentrated, and chromatographed as before, eluting with a linear gradient of methanol-acetonitrile-water running from 40:40:20 to 95:95:10. Appropriate fractions containing pure A83543D were combined, evaporated, dissolved in *t*-butanol, and lyophilized. Both A83543A and A83543D crystallized from aqueous ethanol.

Physical Chemical Characterization of A83543 Factors

The major factor of the complex, A83543A, was determined to have the molecular formula of $C_{41}H_{65}NO_{10}$ and a molecular weight of 731 by high resolution mass spectrometry. The second most abundant factor, A83543D, had the formula of $C_{42}H_{67}NO_{10}$ (MW 745). Among the minor factors, A83543G was isomeric with A83543A, while factors B, E, F, H, and J possessed the formula $C_{40}H_{63}NO_{10}$ (MW 717) and A83543C had the formula $C_{39}H_{61}NO_{10}$ (MW 703). By the use of MS/MS techniques, factors A, D, E, F, H, and J were found to contain the aminosugar forosamine, previously known in the macrolide antibiotic, spiramycin (*26*). A83543G contained a different aminosugar, ossamine, previously known in the fermentation-derived product, ossamycin (*27*). Also isolated was a pseudoaglycone, lacking forosamine but containing the other saccharide substituent of A83543A, which had the formula $C_{33}H_{50}O_9$ (MW 590).

A83543A possessed a chromophore at 243 nm ($\varepsilon = 9000$) in ethanol solution; no changes were observed upon acidification or alkalization. Its only titratable group was the amino group of the aminosugar (pKa = 7.8 in 66% aqueous DMF). It was soluble in most organic solvents, but poorly soluble in water at pH values above 7. It was soluble in dilute aqueous acid due to salt formation; however, strong acids hydrolyzed the acid-labile 2-deoxysugar, forosamine. All of the other factors possessed analogous properties.

Most of the individual factors were separated on the analytical HPLC system described above, with the following retention times (in minutes): Pseudoaglycone (2.55), A83543C (2.62), A83543B (4.22), A83543H (5.29), A83543G (6.49), A83543E (6.57), A83543A (8.97) and A83543D (11.62). A83543F was not well resolved from A83543H and appeared as a poorly resolved shoulder eluting after A83543H.

Elucidation of Structure of A83543A

The gross structural framework of A83543A and its pseudoaglycone was determined from detailed analyses of the physical chemical data described above, mass spectral fragmentation patterns, and extensive NMR investigations, including ^1H homonuclear decouplings, ^{13}C DEPT experiments, 2D one-bond heteronuclear correlations, and 2D long-range heteronuclear correlations (FULCOUP). The relative stereochemistry of the protons at carbon atoms 3, 4, 7, 11, and 12 were established from their coupling constants and from difference NOE experiments.

Both A83543A and its pseudoaglycone crystallized from ethanol-water to give white crystals that were amenable to single crystal X-ray diffraction studies. The crystallographic results confirmed the structural features that had been deduced from mass spectrometry and NMR assignments and established the relative stereochemistry of the substituents at carbon atoms 9, 16, 17, and 21.

The absolute stereochemistry was determined by comparing samples of forosamine obtained from acidic hydrolysis of A83543A and spiramycin. The two samples were identical in all respects, including the sign and magnitude of optical rotation. Consequently, A83543A contained D-(+)-forosamine, as previously determined for spiramycin (*28*). Combining this information with the X-ray results, the absolute configuration of A83543A was determined to be that depicted in Figure 1 (*29*).

Searches of the literature failed to uncover any closely related compounds, indicating that A83543 possesses a very unique structure. The tetracyclic framework is composed of a 5,6,5-*cis-anti-trans*-tricyclic ring system (octahydro-*as*-indacene) fused to a 12-membered macrolide ring. An α,β-unsaturated ketone and an isolated double bond are embedded within the tetracyclic framework. The tetracyclic moiety is substituted at opposite ends by two hydroxyl groups, which are glycosylated with an aminosugar (forosamine) and a neutral sugar (tri-O-methylrhamnose), respectively. The most closely related, previously known compounds found in the literature are spiramycin (which also contains forosamine), ikarugamycin, and capsimycin (see Figure 2). Although ikarugamycin also contains a 5,6,5-*cis-anti-trans*-tricyclic ring system, its absolute stereochemistry is opposite to that of A83543 (*30*). Furthermore, the tricyclic rings of ikarugamycin are fused onto a 16-membered lactam into which a tetramic acid moiety is embedded, whereas the tricyclic rings of A83543 are fused to a 12-membered lactone. In addition, the pattern and type of substituents located around the tricyclic ring systems of ikarugamycin and A83543 are completely different. Finally, A83543 possesses two saccharide substituents while ikarugamycin contains none. The structure of capsimycin has been reported to be similar to that of ikarugamycin (*31*).

Elucidation of Structure of Other Factors

After the structure of A83543A had been established, structures for the remaining factors were readily assigned by comparative analyses of NMR and mass spectral data. It was determined from their empirical formulas and N-methyl NMR resonances that A83543B and A83543C differed from A83543A due to the absence of either one or both N-methyl groups, respectively (*29*). A83543D differed from factor A due to the presence of a methyl substituent attached at carbon 6 on the isolated double bond (*29*). A83543E differed from A83543A due to a methyl rather than an ethyl

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

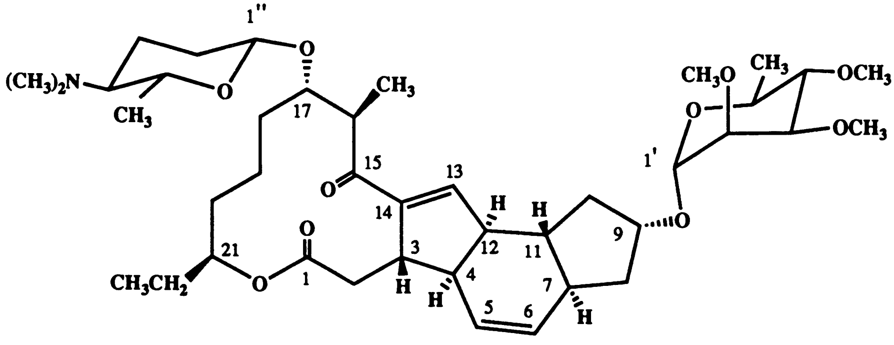

1''
(CH3)2N
CH3
O
O
17
CH3
15
13
O
14
H
H
CH3O
CH3
OCH3
O
OCH3
1'
O
9
O
21
3
12
11
CH3CH2
O
1
H
H
4
7
5
6
H

Figure 1. Absolute configuration and numbering of A83543A

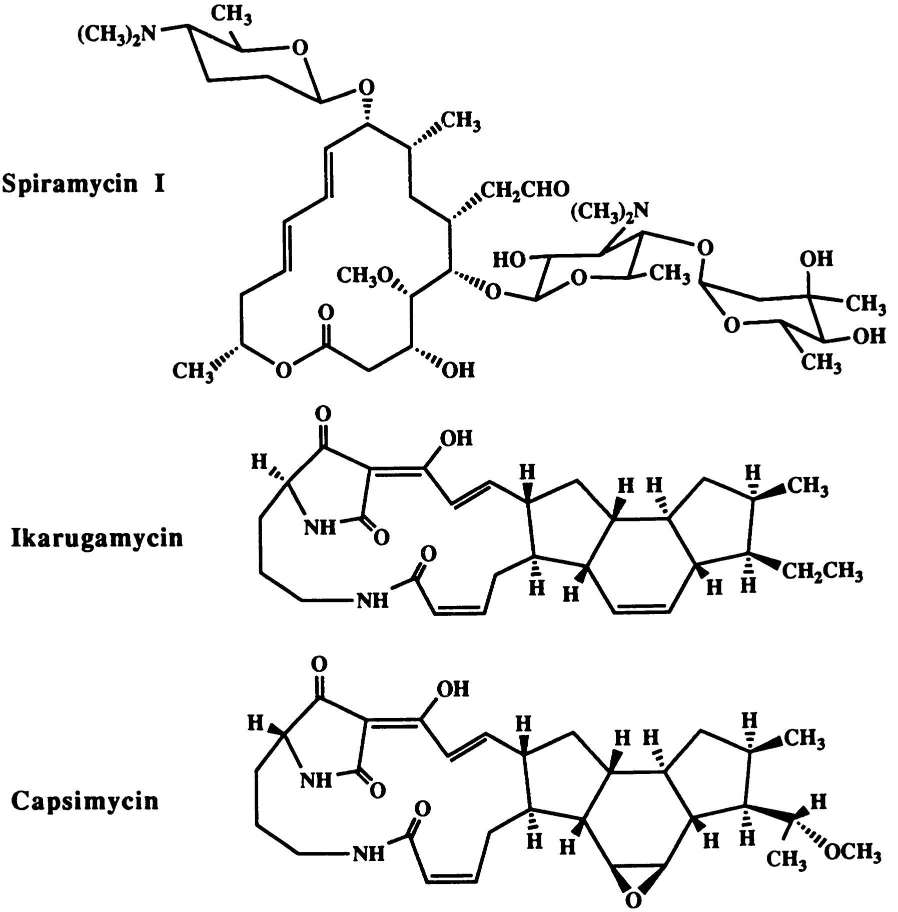

Spiramycin I
(CH3)2N
CH3
O
O
CH3
CH2CHO
(CH3)2N
HO
O
CH3
O
OH
CH3O
O
CH3
OH
O
CH3
O
OH
CH3
Ikarugamycin
O
OH
H
NH
O
H
H H
H
CH3
O
NH
H H
H H
CH2CH3
Capsimycin
O
OH
H
NH
O
H
H H
H
CH3
O
H
NH
H H
H H
CH3
OCH3
O

Figure 2. Structures of spiramycin I, ikarugamycin, and capsimycin

substituent at carbon 21, while A83543F differed from A83543A due to the absence of the methyl group at carbon 16. The structures of factors D, E, and F are readily explained from considerations of the biosynthetic pathway, discussed below.

A83543G differed in that the 17-hydroxyl group of the pseudoaglycone was glycosidated by ossamine rather than forosamine. A83543H and A83543J were determined to be the 2'-O-demethyl and 3'-O-demethyl derivatives of A83543A, respectively. Factors H and J probably arise from incomplete O-methylation of the neutral saccharide moiety at some step in the biosynthetic pathway. The exact sequence of glycosidation and methylation of the two saccharides is a subject of further investigation.

The structures of these nine factors are illustrated in Figure 3. From the variations in structure of these factors, they represent a variety of modifications of N-, C-, and O-methylation in the structure of A83543A.

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

Biological Activity

The purified components of the A83543 complex were tested for activity against fourth instar larvae of the mosquito, *Aedes aegypti*. Mortality after 24 hr at a dose of 0.312 ppm was 60% for A83543A, A83543B, and A83543C; 30% for A83543D; and 80% for A83543E. A83543F and A83543G were not active at this concentration. A83543H and A83543J were also less active than A83543A.

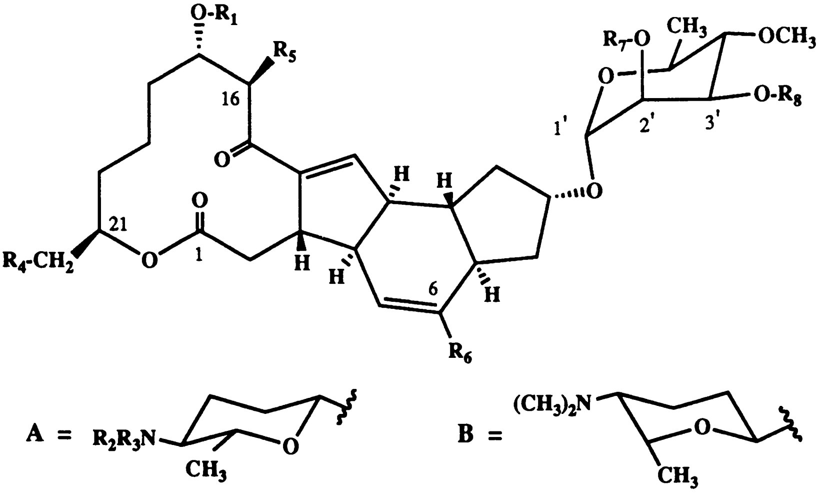
Titration of the dose of A83543A required to kill first instar mosquito larvae revealed a minimum larvicidal concentration of 0.016 ppm for this compound. This level of activity satisfactorily accounted for the activity observed in the crude fermentation broths, indicating that the individual components responsible for the initial activity had been successfully identified and purified.

The strong mosquito larvicidal activity of the A83543 factors distinguishes them from the more conventional macrolides such as tylosin, spiramycin, and erythromycin, which lack insecticidal activity, but possess potent antimicrobial activity (*32*). In further contrast to these latter macrolide antibiotics, the A83543 factors did not inhibit the growth of Gram-positive bacteria (*Staphylococcus, Streptococcus*). Inhibition of Gram-negative bacteria (*Enterobacteriaceae, Pseudomonas*) was also not observed. Other biological activities associated with these compounds will be reported elsewhere.

Biosynthesis of A83543

Based upon incorporation studies using ^{13}C-labeled acetate, propionate, butyrate, and isobutyrate, the biosynthesis of A83543 is consistent with the initial formation of a long chain fatty acid via a polyketide-derived pathway (*33*). Butyrate was apparently cleaved to acetate since it showed the same incorporation pattern as the latter. No enrichment was observed with isobutyrate. The O- and N-methyl groups of the saccharides were

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020


O-R1
R5
16
O
O
21
R4-CH2
O
1
H
H
H
H
6
H
R6
R7-O
CH3
OCH3
O-R8
O
1'
2'
3'
O
A =
R2R3N
O
CH3
B =
(CH3)2N
O
CH3

Factor	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
A	A	CH_3	CH_3	CH_3	CH_3	H	CH_3	CH_3
B	A	CH_3	H	CH_3	CH_3	H	CH_3	CH_3
C	A	H	H	CH_3	CH_3	H	CH_3	CH_3
D	A	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
E	A	CH_3	CH_3	H	CH_3	H	CH_3	CH_3
F	A	CH_3	CH_3	CH_3	H	H	CH_3	CH_3
G	B	--	--	CH_3	CH_3	H	CH_3	CH_3
H	A	CH_3	CH_3	CH_3	CH_3	H	H	CH_3
J	A	CH_3	CH_3	CH_3	CH_3	H	CH_3	H

Figure 3. Structures of individual factors in the A83543 complex

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

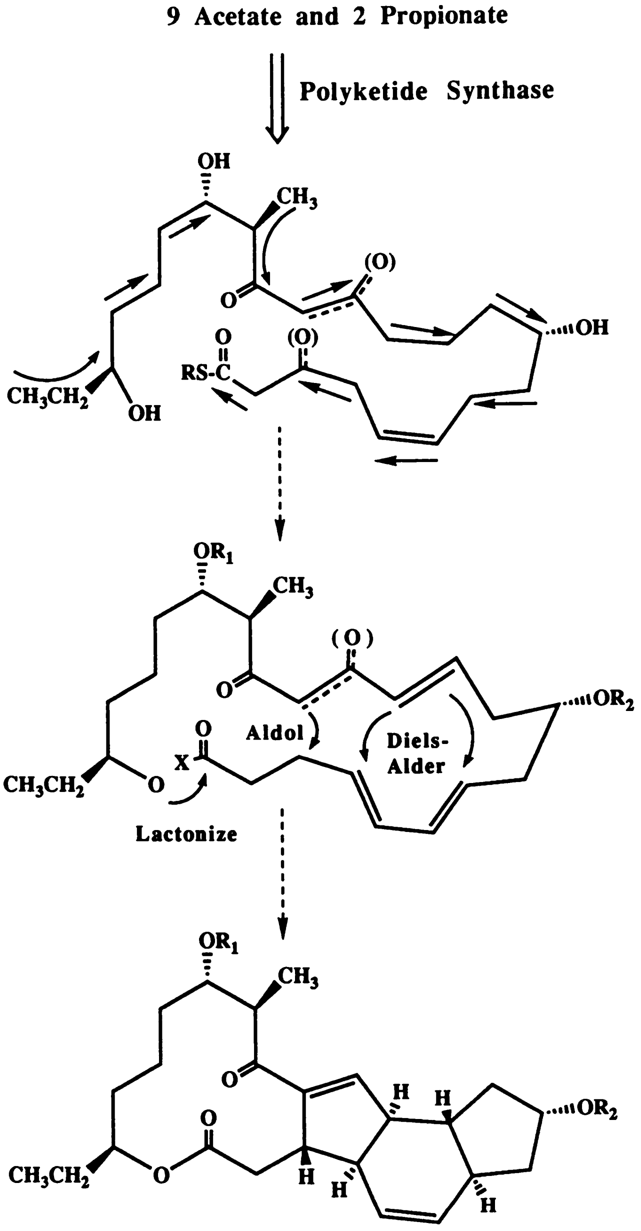

9 Acetate and 2 Propionate
Polyketide Synthase
OH
CH3
(O)
O
(O)
RS-C
O
....OH
CH3CH2
OH
OR1
CH3
(O)
O
....OR2
O
Aldol
Diels-Alder
X
CH3CH2
O
Lactonize
OR1
CH3
O
H
H
....OR2
O
CH3CH2
O
H
H
H

Figure 4. Proposed biosynthetic pathway for A83543A

exclusively labeled by methyl-^{13}C-methionine, probably via S-adenosyl methionine.

Initial formation of a long chain fatty acid is analogous to the well established biosynthetic pathway for monocyclic macrolide antibiotics such as erythromycin and tylosin (*34*). This pathway readily accounts for factors D, E, and F. A83543D arises from the substitution of propionate for acetate at the appropriate point during chain-elongation on the polyketide synthase, and A83543F arises when acetate substitutes for propionate at another point in the cycle. A83543E results when the starter unit for the polyketide synthase is acetate rather than propionate.

In contrast to the monocyclic macrolide antibiotics, biosynthesis of the A83543 tetracyclic ring system also requires the formation of three intramolecular carbon-carbon bonds in addition to lactonization. Two of these carbon-carbon bonds are likely to be formed by an intramolecular Diels-Alder reaction and the third by an intramolecular Aldol condensation and subsequent dehydration and reduction (see Figure 4). The exact sequence of these three ring-forming reactions (lactonization, Diels-Alder, Aldol) has not yet been established. Intramolecular Diels-Alder reactions have previously been proposed in the biosynthesis of other polyketide-derived fermentation products such as ikarugamycin (*30*) and nargenicin (*35*). Further studies are now in progress to determine the steps in the biosynthesis of A83543 that occur after formation of the long chain fatty acid (*36*).

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

Acknowledgments

The authors extend their deep appreciation to their numerous colleagues within the research laboratories of Eli Lilly and Company and DowElanco who helped in the course of this project. We especially thank D. K. Baisden, P. J. Baker, D. M. Berry, L. W. Crandall, L. C. Creemer, V. M. Daupert, T. E. Eaton, T. K. Elzey, O. W. Godfrey, N. D. Jones, J. W. Martin, F. P. Mertz, and D. W. Norton and their associates for their excellent technical assistance and support.

Literature Cited

1. Silver, L.; Bostian, K. *Eur. J. Clin. Microbiol. Infect. Dis.* **1990**, *9*, 455-465.
2. Omura, S. In *Biology of Actinomycetes '88*; Okami, Y.; Beppu, T.; Ogawara, H., Eds.; Japan Scientific Societies Press: Tokyo, Japan, 1988; pp 26-31.
3. *Novel Microbial Products for Medicine and Agriculture*; Demain, A. L.; Somkuti, G. A.; Hunter-Cevera, J. C.; Rossmoore, H. W., Eds.; Elsevier: Amsterdam, The Netherlands, 1989.
4. Umezawa, H. *Rev. Infect. Dis.* **1987**, *9*, 147-164.
5. Tomoda, H.; Omura, S. *J. Antibiotics* **1990**, *43*, 1207-1222.
6. *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: Orlando, Fla., 1984.

7. Monaghan, R. L.; Tkacz, J. S. *Annu. Rev. Microbiol.* **1990**, *44*, 271-301.
8. Zilberman, D.; Schmitz, A., Casterline, G.; Lichtenberg, E.; Siebert, J. B. *Science* **1991**, *253*, 518-522.
9. Pickett, J. A. *Chem. Britain* **1988**, 137-142.
10. Heisey, R. M.; Mishra, S. K.; Putnam, A. R.; Miller, J. R.; Whitenack, C. J.; Keller, J. E.; Huang, J. In *Biologically Active Natural Products: Potential Use in Agriculture*; Cutler, H. G., Ed.; ACS Symposium Series No. 380; American Chemical Society: Washington, DC, 1988; pp 65-78.
11. Fabre, B.; Armau, E.; Etienne, G.; Legendre, F.; Tiraby, G. *J. Antibiotics* **1988**, *41*, 212-219.
12. Neumann, R.; Peter, H. H. *Experientia* **1987**, *43*, 1235-1237.
13. Ando, K. In *Pesticide Chemistry: Human Welfare and the Environment*; Takahashi, N.; Yoshioka, H.; Misato, T.; Matsunaka, S., Eds.; Pergamon Press: Oxford, England, 1983; Vol. 2, pp 253-260.
14. Deshpande, B. S.; Ambedkar, S. S.; Shewale, J. G. *Enzyme Microb. Technol.* **1988**, *10*, 455-473.
15. Burg, R. W.; Stapley, E. O. In *Ivermectin and Abamectin*; Campbell, W. C., Ed.; Springer-Verlag: New York, N.Y., 1989; pp 24-32.
16. Blumauerova, M.; Kristufek, V.; Jizba, J.; Sedmera, P.; Beran, M.; Prikrylova, V.; Stary, J.; Kucera, M.; Sajdl, P.; Landa, V.; Kandybin, V. N.; Samoukina, G. V.; Bortnik, N. I.; Barbashova, N. M. *Prog. Indust. Microbiol.* **1989**, *27*, 237-252.
17. Mrozik, H.; Eskola, P.; Linn, B. O.; Lusi, A.; Shih, T. L.; Tischler, M.; Waksmunski, F. S.; Wyvratt, M. J.; Hilton, N. J.; Anderson, T. E.; Babu, J. R.; Dybas, R. A.; Preiser, F. A.; Fisher, M. H. *Experientia* **1989**, *45*, 315-316.
18. Dybas, R. A.; Hilton, N. J.; Babu, J. R.; Preiser, F. A.; Dole, G. J. In *Novel Microbial Products for Medicine and Agriculture*; Demain, A. L.; Somkuti, G. A.; Hunter-Cevera, J. C.; Rossmoore, H. W., Eds.; Elsevier: Amsterdam, The Netherlands, 1989; pp 203-212.
19. Dybas, R. A.; Babu, J. R. In *British Crop Protection Conference - Pests and Diseases*; British Crop Protection Council: Croyden, U. K., 1988; pp 57-64.
20. *W. H. O. Technical Report Series*, Number 265; World Health Organization: Geneva, Switzerland, 1963.
21. Brown, A. W. A.; Pal, R. *Insecticide Resistance in Arthropods*, 2nd ed.; World Health Organization: Geneva, Switzerland, 1971.
22. Nickerson, K. W.; Schnell, D. J. *J. Invertebr. Pathol.* **1983**, *42*, 407-409.
23. Mishra, S. K.; Keller, J. E.; Miller, J. R.; Heisey, R. M.; Nair, M. G.; Putnam, A. R. *J. Indust. Microbiol.* **1987**, *2*, 267-276.
24. Mertz, F. P.; Yao, R. C. *Int. J. Syst. Bacteriol.* **1990**, *40*, 34-39.
25. Kirst, H. A.; Michel, K. H.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Thompson, G. D. In *Dev. Indust. Microbiol. Series; Microbial Metabolites #2;* Nash, C. H., Ed.; William C. Brown Publishers: Essex, Ct., 1992.

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

26. Omura, S.; Nakagawa, A.; Neszmelyi, A.; Gero, S. D.; Sepulchre, A.-M., Piriou, F.; Lukacs, G. *J. Amer. Chem. Soc.* **1975**, *97*, 4001-4009.
27. Stevens, C. L.; Gutowski, G. E.; Bryant, C. P.; Glinski, R. P.; Edwards, O. E.; Sharma, G. M. *Tetrahedron Lett.* **1969**, 1181-1184.
28. Albano, E. L.; Horton, D. *Carbohyd. Res.* **1969**, *11*, 485-495.
29. Kirst, H. A.; Michel, K. H.; Martin, J. W.; Creemer, L. C.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Jones, N. D.; Thompson, G. D. *Tetrahedron Lett.* **1991**, *32*, 4839-4842.
30. Ito, S.; Hirata, Y. *Bull Chem. Soc. Japan* **1977**, *50*, 1813-1820.
31. Seto, H.; Yonehara, H.; Aizawa, S.; Akutsu, H.; Clardy, J.; Arnold, E.; Tanabe, M.; Urano, S. *Chem. Abstr.* **1979**, *92*, 211459u.
32. Kirst, H. A. *Ann. Rep. Med. Chem.* **1990**, *25*, 119-128.
33. Nakatsukasa, W. M.; Mabe, J. A.; Michel, K. H.; Martin, J. W.; Paschal, J. W.; Elzey, T. K. *Abstracts of 2nd Int'l. Conf. on Biotechnology of Microbial Prod.* **1990**, P-21.
34. Omura, S.; Tanaka, Y. In *Biotechnology*; Rehm, H.-J.; Reed, G., Eds.; VCH: Weinheim, Germany, 1986; Vol. 4, *Microbial Products II*; Pape, H.; Rehm, H.-J., Vol. Eds.; pp 359-391.
35. Cane, D. E.; Yang, C.-C. *J. Amer. Chem. Soc.* **1984**, *106*, 784-787.
36. Broughton, M. C.; Huber, M. L. B.; Creemer, L. C.; Kirst, H. A.; Turner, J. R. *Abstracts of Amer. Soc. Microbiol. Annual Mtg.* **1991**, K58.

RECEIVED April 27, 1992

Downloaded by OHIO STATE UNIV LIBRARIES on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch020

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

Chapter 21

New Series of Milbemycin Macrolides (LL-F28249) with Endectocidal, Insecticidal, and Acaricidal Activity

Synthetic Modification and Biological Activity

T. C. Barden, G. Asato, Z. H. Ahmed, D. J. France, V. Kameswaran, E. Parker-Jackson, S. Y. Tamura, S-S. Tseng, and B. L. Buckwalter

**Agricultural Research Division, American Cyanamid Company,
P.O. Box 400, Princeton, NJ 08543–0400**

LL-F28249 is a new series of 16-membered macrolides recently isolated from *S. cyanogriseus* by the Medical Research Division of American Cyanamid. Several features of this series distinguish it from the related milbemycins and avermectins. The chemical modification of F28249α, the major component of fermentation broths, is described. The chemistry focuses on the unique characteristics of LL-F28249. The endectocidal, acaricidal and insecticidal activity of representative F28249α derivatives also is presented.

Since the discovery of the milbemycins from *Streptomyces hygroscopicus* by Sankyo researchers in 1974 many other members of this class of macrolides have been reported from a variety of *Streptomyces* species (*1*). All milbemycins contain a 16-membered macrolide ring and a spiroketal moiety although considerable diversity is seen around the periphery of the ring. It is not possible in the space available to comprehensively review all the isolation, characterization and synthetic research in this area. Rather, this introduction attempts briefly to place the current work into proper context and to provide key references and reviews for those interested in further information (*2-4*).

Milbemycin D **1** is typical of the materials produced by *S. hygroscopicus*. Others are further oxidized at C(22), C(23), C(4α), or C(5). In a few cases the tetrahydrofuranyl ring is incomplete or C(2-7) may be aromatized. A variety of pendant alkyl groups are found at C(12), C(24) and C(25) (*5,6*).

S. avermitilis, first characterized by chemists at Merck in 1978, produces a group of glycosylated milbemycins (2). Avermectin B_{1a} **2** typifies this group of milbemycins which is further oxidized at C(13) and contains an α-L-oleandrosyl-α-L-oleandrosyl disaccharide at this position. The major series, A_1 and B_1, are

0097–6156/92/0504–0226$06.00/0

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

unsaturated at C(22, 23) although hydroxylation at C(23) is seen in the A_2 and B_2 series. Other structural variations found in this series parallel those in the rest of the milbemycins. The entire family of milbemycin natural products recently has been reviewed (*3,4*).

In 1984 Carter et al. in the Medical Research Division of American Cyanamid isolated a new series of milbemycins from *S. cyanogriseus* (*7*). The distinguishing feature of these compounds, designated F28249, is a C(25) alkenyl substituent. The series is exemplified by F28249α **3**, the main component in fermentation broths. The C(23) position of all components is hydroxylated; no $\Delta^{22,23}$ or C(23)-dehydroxy variants are present. Various alkyl substitution is present at the C(25) olefin terminus or at C(12). Still other structural modifications are similar to those produced by *S. hygroscopicus* and *S. avermitilus* (*3*).

Shortly after the Cyanamid discovery, Glaxo researchers isolated the same series, in their nomenclature S541, from *S. thermoarchaensis* (*8*). Factor A of this series is identical to F28249α. For several years both Cyanamid and Glaxo had active programs modifying and testing derivatives of F28249α. Some of the work followed parallel avenues and several reports of the Glaxo work have appeared. This paper describes research carried out at American Cyanamid's Agricultural Research Division in Princeton, New Jersey.

Novel series of milbemycins still are being isolated. Researchers at SmithKline Beecham recently have described another group of C(25) olefinated milbemcycins which are generally hydroxylated at C(22) (*9*). In another approach, researchers at Pfizer detail the isolation and characterization of novel milbemycins by combining the techniques of directed biosynthesis and molecular biology (*10*).

Although the milbemycins are weak antibiotics, they are quite active in several other areas. The high insecticidal and acaricidal activity of this family was discovered by Sankyo (*1, 5, 6*). Merck subsequently found that these macrolides are potent anthelmintics and possess anti-ectoparasitic properties as well (*11-13*). Merck's Ivermec became the prototype for a new generation of antiparasitic agents with broad endo- and ectoparasitic activity.

The structure/activity relationship of various avermectin and milbemycin derivatives has been widely explored and described (*2*). However, many portions of the macrolide ring are not easily functionalized and the effect of modification here on the biological activity is unknown. The F28249 series also affords access to many compounds not readily available from other members of this macrolide class. This report describes some of the chemical transformations unique to this series and the surprising range of biological activity exhibited by F28249 analogs.

Protection Strategies

The early work at Merck suggested that the three hydroxyls at C(7), C(5) and C(23) could be independently manipulated (*14*). Except for a tendency to eliminate, the sterically hindered C(7) alcohol is essentially inert. It usually can be ignored in designing synthetic plans. Although the two remaining alcohols are both secondary, the C(5) hydroxyl can be acetylated, silylated or oxidized selectively under very mild conditions.

The silylation regioselectivity is dependent on the leaving group of the reagent (Figure 1). With *t*-butyldimethylsilyl chloride silylation occurs preferentially at the C(5) hydroxyl (**3**→**4**) whereas silylation at the C(23) hydroxyl predominates with *t*-butyldimethylsilyl triflate (**3**→**5**). Although C(5) is more accessible

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

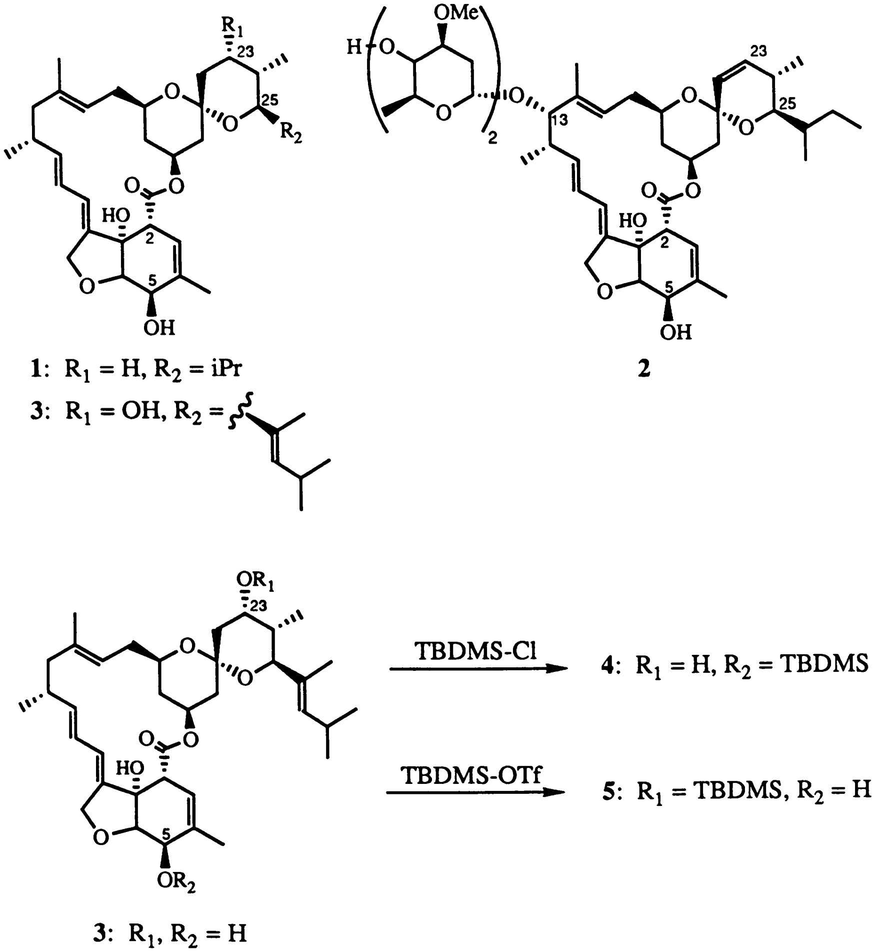

R1
23
25
R2
O
O
O
O
HO
2
5
OH
1: R1 = H, R2 = iPr
3: R1 = OH, R2 =
OMe
H
O
O
O
2
13
23
25
O
O
O
O
HO
2
5
OH
2
OR1
23
O
O
O
O
HO
5
OR2
3: R1, R2 = H
TBDMS-Cl
4: R1 = H, R2 = TBDMS
TBDMS-OTf
5: R1 = TBDMS, R2 = H

Figure 1. Site selectivity for TBDMS-Cl vs TBDMS-OTf.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

sterically, the C(23) oxygen is more basic due to hydrogen bonding to the C(17α) oxygen. Apparently, the tightly bound chloride is too large to allow kinetic silylation of the C(23) position resulting in C(5) silylation. The silyl triflate is effectively dissociated leaving a less encumbered silicon to silylate the inherently more reactive C(23) hydroxyl. Glaxo has reported that the C(5)/C(23) regioselectivity of acylations is a function of the reagent used (*8*).

Treatment with *p*-toluenesulfonic acid cleaves the C(5) silyl ether while base removes a C(5) acetate protecting group. Selective protection and deprotection of C(5) and C(23) is thus readily accomplished.

Silyl ethers at C(23) also are easily cleaved with *p*-toluenesulfonic acid but esters at this position generally are not. The lactone carbonyl is more susceptible to attack by base than most C(23) esters. A notable exception to this is the C(23) methyl oxalate ester **6**, easily prepared from the C(5) acetate. Brief treatment of **6** with base at -10 °C selectively removes the C(23) ester (Figure 2). Removal of the C(5) acetate requires somewhat higher temperature and longer time but still proceeds in high yield.

Diester **6** is a useful intermediate for many types of target analogs when the reagents needed are not compatible with alcohol groups. After a remote part of the molecule is functionalized, the alcohols at C(23) and C(5) can be sequentially deprotected and selectively derivatized if desired.

C(23) Modification

Once C(5) has been protected a wide variety of chemistry can be performed at C(23) leading to novel and active F28249α derivatives. In some cases protection of C(5) is unnecessary.

Dehydration to either the $\Delta^{22,23}$ or $\Delta^{23,24}$ alkene can be accomplished from F28249α (Figure 3). Pyrolysis of xanthate **8** in refluxing *o*-dichlorobenzene cleanly gives $\Delta^{22,23}$ olefin **9**. The analogous elimination has been demonstrated in the avermectin series (*15*). Alternatively, $\Delta^{23,24}$ dehydration results from treating a C(5)-protected F28249α with diethylaminosulfur trifluoride (DAST) in dimethoxyethane at -78 °C (**7**→**10**). The analog completely unsubstituted at C(23) is obtained by tributyltin hydride/AIBN reduction of **8** (**8**→**11**) or the C(23) β-bromo analog.

The C(23) ketone of F28249α (**12**) is a versatile intermediate. It can be prepared from the C(5) protected material by various standard procedures (Swern Oxidation, Mofatt Oxidation, RuO_4/TPAP, etc.) (*16*).

Alkyl and aryl Grignard reagents add to **12** to generate the corresponding C(23) tertiary alcohols. The yields are high even though a large excess of reagent is required (*16*). The base sensitive macrolide carbonyl in unaffected by the presence of these metal alkyl bases although basic conditions can produce lactone opening, epimerization at C(2), isomerization of $\Delta^{3,4}$ double bond to the $\Delta^{2,3}$ position and aromatization (*17*). Presumably initial formation of the C(7) magnesium alkoxide suppresses reaction at these proximate sites.

The C(23) ketone also readily forms O-alkyl oximino and hydrazone derivatives (*16*). One of these, moxidectin **17**, has been developed by American Cyanamid and has emerged as a promising new anthelmintic product. The surprising range of biological activity shown by these alkoximes and hydrazones will be presented later.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

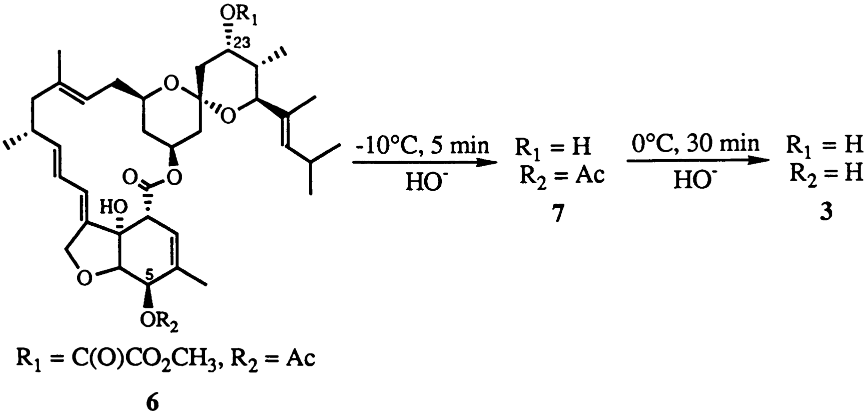

OR1
23
O
O
O
O
HO
5
O
OR2
-10°C, 5 min
HO⁻
R1 = H
R2 = Ac
7
0°C, 30 min
HO⁻
R1 = H
R2 = H
3
R1 = C(O)CO2CH3, R2 = Ac
6

Figure 2. Selective deprotection of 6.

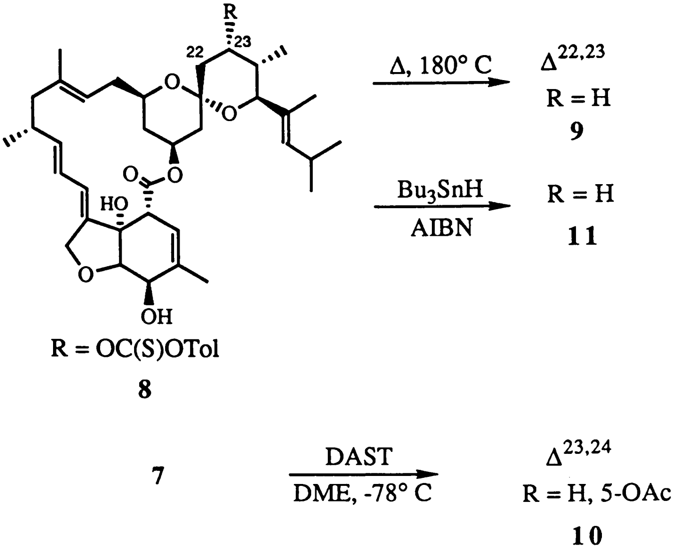

R
22
23
O
O
O
O
HO
O
OH
R = OC(S)OTol
8
Δ, 180° C
Δ22,23
R = H
9
Bu3SnH
AIBN
R = H
11
7
DAST
DME, -78° C
Δ23,24
R = H, 5-OAc
10

Figure 3. Dehydration/reduction of the C(23)-OH

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

C(25) Sidechain Modification

The olefinic sidechain distinguishes the F28249 series from other milbemycins and avermectins. Functionalization of the $\Delta^{26,27}$ olefin affords a unique set of analogs. Halogenation of F28249α with N-chlorosuccinimide (NCS) or N-bromoacetamide (NBA) occurs with rearrangement of the allylic olefin (Figure 4) (*18*). Carefully controlled conditions are required to limit the reaction to the sidechain olefin. The second most reactive olefin is the $\Delta^{14,15}$ position.

Upon treatment with silver salts, the transient allylic carbonium ion is trapped with various nucleophiles, regenerating the starting double bond. Mixtures of E and Z olefin isomers are usually obtained. The reaction works well for a wide range of nucleophiles. Reduction of the allylic halide with tributyltin hydride/AIBN gives back the $\Delta^{26,27}$ olefin.

m-CPBA Epoxidation also is selective for the sidechain olefin. The selectivity between the sidechain and the $\Delta^{14,15}$ position is sensitive to the reaction conditions and the nature and orientation of the C(23) substituent. The sidechain olefin is generally the favored reaction site but this can be completely reversed by certain C(23) groups (Figure 5).

Little insight into the reasons for this substituent dependence is gained from semi-emperical AM1 calculations. The substituent at C(23) has a negligible effect on the conformation of the ring and sidechain (Figure 6). While there is some variation in the calculated electron density of the sidechain carbons with the different groups at C(23), it is small and does not correlate at all with the experimentally determined product ratios. More sophisticated calculations will be needed to fully understand this effect.

C(13) Modification

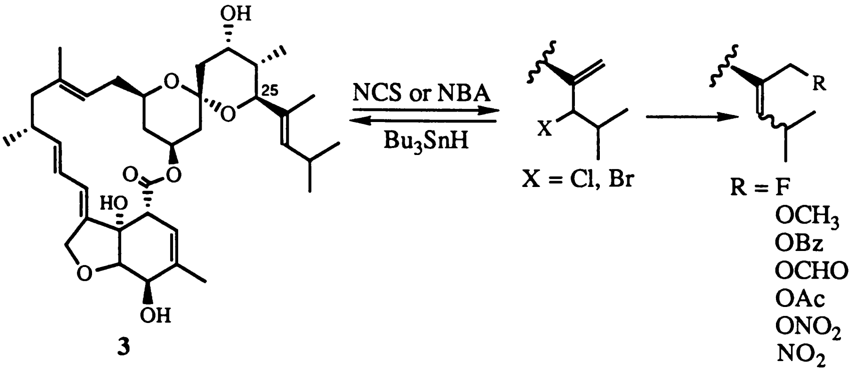
Oxidation of a doubly protected F28249α derivative with SeO_2 in aqueous formic acid selectively gives the 13-β-formate though oxidation of the C(25) sidechain olefin is competitive (Figure 7) (*20*). By careful monitoring the reaction can be stopped before sidechain oxidation products accumulate although unreacted starting material sometimes still remains. The 13-β alcohol can be obtained by hydrolysis of the formate or, alternatively it is produced directly by oxidation with SeO_2 in aqueous trifluoroethanol (TFE). The alcohol gives access to 13-β-halo analogs and 13-β-ethers.

The reactivity of the allylic sidechain is again dependent on the C(23) substituent, suggesting that the same effect which influences epoxidation ratios is operating here as well. With most C(23) substituents oxidation occurs preferentially at the C(13) position before doubly oxidized products appear. The C(23)-dehydroxy derivative gives only slightly selective oxidation at C(13) and monooxidation products at C(13) and C(26α) can be isolated. The C(23) methyl oxalate is the most convenient substrate; the reaction can be allowed to run to completion with minimal overoxidation.

Biological Activity

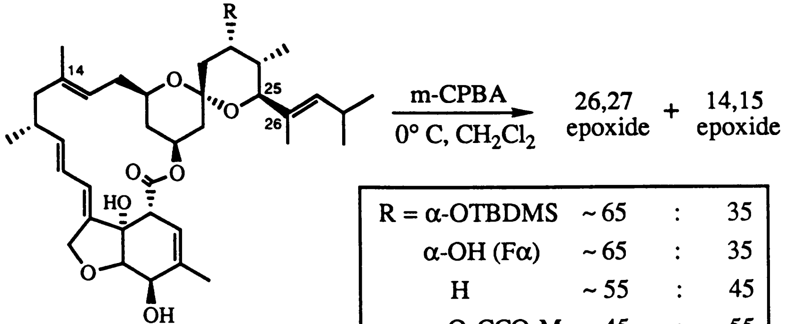
The naturally occurring F28249 macrolides already have potent endo- and ectoparasiticidal and insecticidal activity. A semisynthetic program was initiated to optimize the biological activity. Many synthetic derivatives retained the high biological

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021


OH
25
NCS or NBA
Bu3SnH
X
X = Cl, Br
R
R = F
OCH3
OBz
OCHO
OAc
ONO2
NO2

3

Figure 4. C(25) Sidechain modification of F28249α.


R
14
25
26
m-CPBA
0° C, CH2Cl2
26,27 epoxide
+
14,15 epoxide

R = OH
3

R = α-OTBDMS	~65	:	35
α-OH (Fα)	~65	:	35
H	~55	:	45
α-O_2CCO_2Me	~45	:	55
β-OH	~40	:	60
β-Br	~35	:	65

Figure 5. Influence of C(23) substituent on epoxidation regioselectivity

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

R
H
=O
α - F
α - O_2CCO_2Me
α - OH
β - OH
α - Br
β - Br

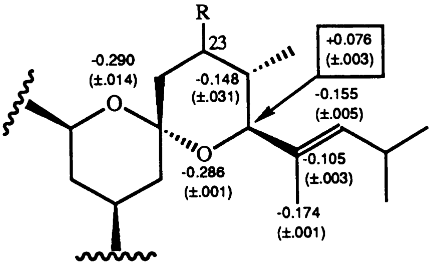

R
23
-0.290
(±.014)
O
-0.148
(±.031)
+0.076
(±.003)
-0.155
(±.005)
O
-0.286
(±.001)
-0.105
(±.003)
-0.174
(±.001)

Figure 6. Variation of electron density with C(23) substitution

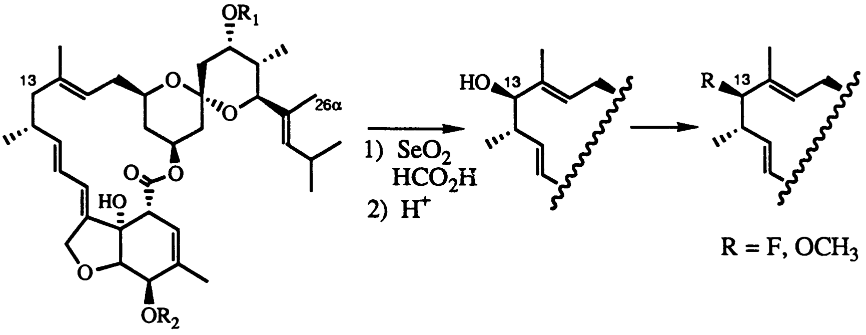

OR_1
13
O
O
26α
O
O
HO
O
OR_2
1) SeO_2
HCO_2H
2) H^+
HO
13
R
13
R = F, OCH_3

Figure 7. Functionalization of C(13)

activity found in the parent or had improved activity. However, the effect of subtle structural changes on the potency of similar analogs is striking.

In the tables which follow the endectocidal and insecticidal profile of analogs is modeled by their activity against representative pest species. The sheep parasite *Trichostrongylus colubriformis* provides a measure of endoparasitic activity while the ectoparasite activity is assessed with the rabbit ear mite *Psoroptes cuniculi*. Representative crop pests are the two-spotted mite *Tetranychus urticae* and southern armyworm *Spodoptera eridania*. Activity against a number of other destructive insect species often is seen as well. The activity in all tables is reported as % kill/control at the indicated dose.

The structural differences between the C(23)-dehydroxy **11** and dehydrated (**9** and **13**) F28249α derivatives is small yet they have a very different endectocidal activity spectrum (Table I). Compared to F28249α, both **9** and **13** have better *T. colubriformis* activity but are less active against *P. cuniculi* whereas **11** has about the reversed activity spectrum. All three derivatives in Table I have improved acaricidal and insecticidal activity over F28249α, but simply changing the position of the double bond substantially changes the potency of **9** and **13** against the last two species.

Although the C(25) sidechain derivatives substituted at C(26α) have poor biological activity overall, epoxidation of the side chain 26,27 double bond considerably improves the activity in certain screens (Table II). Epoxide **14** is much more potent against *T. colubriformis* than **3** but is a less effective ectoparasiticide. Epoxidation at the 14, 15 olefin or double epoxidation causes no such dramatic improvement (**15**, **16**).

The novel 23-imino derivatives were the most promising compounds to be identified. This group included O-alkyl oximes, acylhydrazones, carbazides and semicarbazones. Within the O-alkyl oximes some interesting selectivities were noted. As the size of the alkyl moiety increased the endoparasiticidal activity dropped sharply while the acaricidal, insecticidal and ectoparasiticidal activity remained high (**17** - **20**) (Table III). In contrast, the formyl (**21**) and acetyl (**22**) hydrazones are much more active against *T. colubriformis* and weaker against *P. cuniculi* than the O-alkyl oximes. Moxidectin **17** has the optimal activity spectrum with substantially improved activity than F28249α in all four areas. The precursor to the above derivatives, ketone **12**, retains most of the activity shown by **3** but is a much weaker ectoparasiticide.

Several other classes of derivatives also have improved biological activity over F28249α in one screen or another. These include C(5) esters, C(23) dehydroxy analogs, Grignard adducts from C(23) ketones and C(13) β-ether and β-halides. The C(13) substituted compounds, in particular, are potent broad spectrum endectocides, acaricides and insecticides.

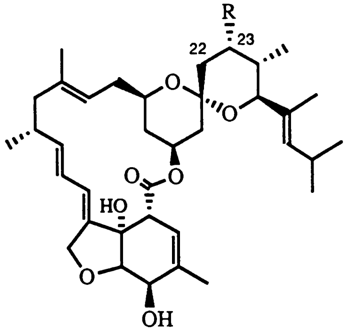
Recent field trials indicate that F28249 has commercial potential as an acaricide. On cotton F28249α gives good control of the two-spotted mite *T. urticae* and broad mite *Polyphagotarsonemus latus* at 30 grams per hectare (Table IV). Addition of a small amount of oil reduces the amount needed to 11 grams per hectare. The oil here may serve several roles (*20*). It might provide some protection from UV degradation and air oxidation, give better plant coverage of the miticide and also aid in penetration of the cuticule.

LL-F28249 is a new series of milbemycins active against many animal parasites and crop pests. The characteristic unsaturated sidechain and uniform hydroxylation of C(23) affords practical access to many novel derivatives.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

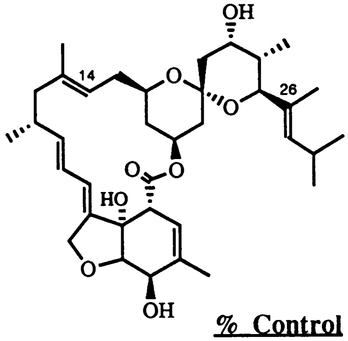
Table I. Testing of C(23) dehydroxy and dehydrated derivatives



% Control

	T. colubriformis (mg/kg)		*P. cuniculi* ($\mu g/cm^2$)		*T. urticae* (ppm)		*S. eridania* (ppm)	
	0.0625	0.0313	1.0	0.1	1.0	0.1	100	10
3: R = OH (F28249α)	88	68	100	93	90	30	80	0
11: R = H	89	44	100	100	100	100	100	100
9: R = H, $\Delta^{22,23}$	100	95	82	81	100	100	100	10
13: R = H, $\Delta^{23,24}$	96	71	85	34	100	30	100	100

Table II. Testing of epoxide derivatives

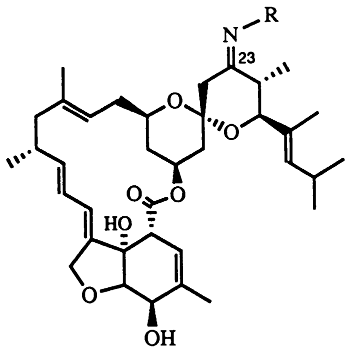


% Control

	T. colubriformis (mg/kg)		*P. cuniculi* ($\mu g/cm^2$)		*T. urticae* (ppm)		*S. eridania* (ppm)	
	0.0625	0.0313	1.0	0.1	1.0	0.1	100	10
3: R = OH (F28249α)	88	68	100	93	90	30	80	0
14: 26,27 epoxide	100	99	< 48	0	100	0	100	0
15: 14,15 epoxide	83	31	31	9	100	100	100	10
16: 14,26 bis-epoxide	95	53	100	43	-	-	100	0

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

Table III. Testing of C(23) imino derivatives



	% Control							
	T. colubriformis (mg/kg)		*P. cuniculi* ($\mu g/cm^2$)		*T. urticae* (ppm)		*S. eridania* (ppm)	
	0.0625	0.0313	1.0	0.1	1.0	0.1	100	10
3 (F28249α)	88	68	100	93	90	30	80	0
17: R = OCH_3	97	81	100	97	100	100	100	100
18: R = OC_2H_5	57	26	100	100	100	100	100	0
19: R = OC_3H_7	< 71	-	100	100	100	100	-	0
20: R = OPh	1	7	100	79	-	-	100	0
21: R = NHC(O)H	100	79	27	12	0	0	10	100
22: R = NHC(O)CH_3	99	90	< 69	-	50	0	100	0
12: C(23) ketone	99	85	< 14	-	100	90	100	30

Table IV. F28249α Control of *T. urticae* and *P. latus* on cotton

	% Control		
	T. urticae		*P. latus*
Test I	6 DAT[a]		6 DAT[a]
10 g/ha	64		81
30 g/ha	93		98
Test II	7 DAT[a]	14 DAT[a]	
34 g/ha	97	93	--
11 g/ha	87	75	--
11 g/ha[b]	98	84	--

a) Days after treatment; b) 2.5 % (v/v) emulsified petroleum oil added.

However, these same features also present new synthetic challenges to the selective modification of this highly funtionalized macrocyclic ring system. The striking and often surprising range of biological activity seen for structurally similar analogs against ectoparasites, endoparasites and destructive crop pests shows that much more work is necessary before the structure/activity relationship of this important class of macrolides is fully understood.

Acknowledgments

The authors would like to gratefully acknowledge Guy Carter for supplies of F28249α, David M. Gange for AM1 calculations, Mary L. Doscher, John Pankavich, Wynn Wood for animal screening, Donald P. Wright for insecticide screening, and Timothy P. Miller, Michael F. Treacy for acaricide field trial testing.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

Literature Cited

1. Mishima, H.; Kurabayashi, M.; Tamura, C.; Sato, S.; Kuwano, H.; Saito A.; Aoki, A. *Abs. Paps.-18th Symp. Chem. Natural Products Kyoto*, Japan **1974**, 309.
2. See Fisher, M. H. and Mrozik, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S. Ed.; Academic Press: San Diego, CA, 1984; pp 553-607 and references cited therein.
3. Davies, H. G.; Green, R. H. Chem. Soc. Rev. **1991**, *20*, 211-269 and references cited therein.
4. *Ibid.* **1991**, *20*, 271-339.
5. Aoki, A.; Fukuda, R.; Nakayabu, T.; Ishibashi, K.; Takeiche, C.; Ishida, M. *J. Antibiot.* **1976**, *29*, 76-14 - 76-16.
6. *Ibid.* **1976**, *29*, 76-35 - 76-42.
7. Carter, G. T.; Nietsche, J. A.; Hertz, M. R.; Williams, D. R.; Siegel, M. M.; Morton, G. O.; James, J. C.; Borders, D. B. *J. Antibiot.* **1988**, *41*, 519-529.
8. Ramsay, M. V. J.; Roberts, S. M.; Russell, J. C.; Shingler, A. H.; Slawin, A. M. Z.; Sutherland, D. R.; Tiley, E. P.; Williams, D. J. *Tetrahedron Lett.* **1987**, *28*, 5353-5356.
9. Hood, J. D.; Banks, R. M.; Brewer, M. D.; Fish. J. P.; Manger, B. R.; Poulton, M. E. *J. Antibiot.* **1989**, *42*, 1593-1598.
10. Dutton, C. J.; Gibson, S. P.; Goudie, A. C.; Holdom, K. S.; Pacey, M. S.; Ruddock, J. C.; Bulock, J. D.; Richards, M. K. *J. Antibiot.* **1991**, *44*, 357-365.
11. Burg, R. W.; Miller, B. M.; Baker, E. E.; Birnbaum, J.; Currie, S. A.; Hartman, R.; Kong, Y.-L.; Monaghan, R. L.; Olson, G.; Putter, I.; Tunac, J. B.; Wallick, H.; Stapley, E. O.; Oiwa, R.; Omura, S. *Antimicrob. Agents Chemother.* **1979**, *15*, 361-367.
12. Miller, T. W.; Chaiet, L.; Cole, D. J.; Cole, L. J.; Flor, J. E.; Goegelman, R. T.; Gullo, V. P.; Kempf, A. J.; Krellwitz, W. R.; Monaghan, R. L.; Ormond, R. E.; Wilson, K. E.; Albers-Schoenberg, G.; Putter, I. *Ibid.* **1979**, *15*, 368-371.
13. Egerton, J. R.; Ostlind, D. A.; Blair, L. S.; Eary, C. H.; Suhayda, D.; Cifelli, S.; Riek, R. F.; Campbell, W. C. *Ibid.* **1979**, *15*, 372-378.
14. Mrozik, H.; Eskola, P.; Fisher, M. H.; Egerton, J. R.; Cifelli, S.; Ostlind, D. A. *J. Med. Chem.* **1982**, *25*, 658-663.
15. Mrozik, H. H. (Merck and Co., Inc.) US Patent, 4 550 160, **1979**.

16. cf. Beddall, N. E.; Howes, P. D.; Ramsay, M. V. J.; Roberts, S. M.; Slawin, A. M. Z.; Sutherland, D. R.; Tiley, E. P.; Williams, D. J. *Tetrahedron Lett.* **1988**, *29*, 2595-2598.
17. Pivnichny, J. V.; Shim, J.-S. K.; Zimmerman, L. A. *J. Pharm. Sci.* **1983**, *72*, 1447-1450.
18. cf. Burckhardt, U. (Ciba-Geigy Corp.) US Patent, 4 584 314, 1986; European Patent, 143 747, 1984.
19. Sato, K.; Kinoto, T.; Mio, S.; Yanai, T. (Sankyo Company, Ltd.) US Patent, 4 835 290.
20. Treacy, M. F.; Southwick, L. M.; Benedict, J. H. In *Influence of Oils on the Fate and Efficacy of Insecticides*; Benedict, J. H., Treacy, M. F.; Kinard, D. Eds.; *Use of Cottonseed and Other Vegetable Oils with Agrichemicals*; National Cotton Council: Memphis, Tennessee, 1992, submitted.

RECEIVED April 9, 1992

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch021

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

Chapter 22

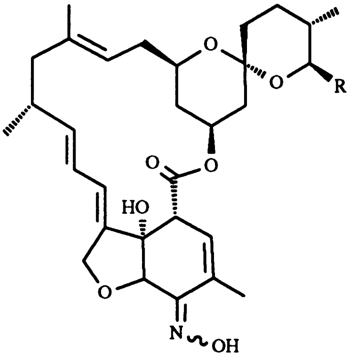
Regio- and Stereoselective Synthesis of 13β-Substituted-milbemycins, Including the 13β-Alkyl-milbemycins

Anthony C. O'Sullivan and Bruno Frei

Plant Protection Division, Ciba-Geigy Ltd., CH–4002 Basel, Switzerland

The synthesis of 13β-substituted milbemycins including 13β-alkyl milbemycins was examined in some detail. After establishing the SN_1 reaction as the prefered method of introduction of substituents at the 13β position, it was found that the optimal synthesis of 13β-ethyl-milbemycin A_4 **20B** involves a novel *syn* 1,3 reaction of 15-chloro-Δ13,14-milbemycin A_4 **22B** with triethyl aluminium. Another new alkylation reaction using a nickel or cobalt catalysed reaction of dialkyl zinc with 13β-bromo-milbemycin A_4 **14B**, involving a radical intermediate, was developed. Biological results are discussed.

The milbemycins are a family of 16-membered ring macrolides, isolated by Sankyo chemists in 1973 (*1*), which possess potent anthelmintic, acaricidal, and insecticidal activity (2)(Table 1). The avermectins are compounds with similar structures and biological activity as the milbemycins, which were isolated later by workers at Merck, Sharp, and Dohme (*3*), who have commercialised a mixture of 22,23 dihydroavermectin B1a and B1b in 1981 as an antiparasitic agent under the generic name Ivermectin (*4*)(Table 1). The interesting chemical structures of this class have generated an enormous effort towards the total synthesis of these compounds (*5*), and the novel mode of action (*6*) and potent biological activity have attracted large industrial interest (*7*).



R= Et(>80%),Me(<20%)

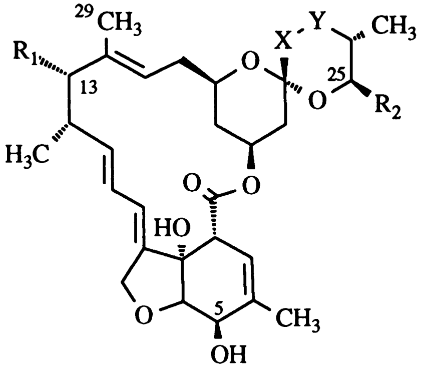
Interceptor

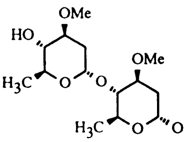
0097–6156/92/0504–0239$06.00/0

A few years after the introduction of Ivermectin to the market, Ciba-Geigy and Sankyo started work on a joint derivatisation program, seeking to optimise the anthelmintic activity of the milbemycins. For strategic purposes, at the beginning of the joint project, the research was divided between the two groups, with Ciba-Geigy treating the top half of the molecule, and Sankyo the bottom half, in particular the hydroxy group at C(5). Sankyo's early work led to the discovery of the heart worm activity of the C(5)-oxime, and its introduction in 1990 into the market under the trade name Interceptor. Ciba-Geigy's initial effort resulted in the derivatisation of several positions in the upper part of the molecule (e.g. position 29 (*8*)). We describe here the functionalisation and derivatisation of C(13), in particular the alkyl derivatives.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

Table I. Structures of Milbemycins and Avermectins



No	Name	R_1	R_2	X-Y
1A	Milbemycin A_3	H	Me	CH_2-CH_2
1B	Milbemycin A_4	H	Et	CH_2-CH_2
1D	Milbemycin D	H	*i*-Pr	CH_2-CH_2
2	Avermectin B_{1a}		*s*-Bu	CH=CH
3	Avermectin B_{1b}		*i*-Pr	CH=CH
4I	Ivermectin		*s*-Bu:*i*-Pr 80:20	CH_2-CH_2
5I	Ivermectin aglycone	OH	*s*-Bu:*i*-Pr	CH_2-CH_2

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

By compounds numbers with **A**,**B**,**D**, and **I**, we refer to derivatives of milbemycin A_3, A_4, D, and 22,23 dihydroavermectin respectively. The series differ at the C(25) alkyl group. However, this group is chemically quite inert and remote from the part of the molecule which is the subject of this paper. We have continually observed comparable results in reactions in the region of C(13) of the three milbemycins [C(25) = Me,Et, and iPr] and two ivermectins [C(25) = iPr and iBu]. The reader may thus safely ignore the lettering part of the numeration, which we are forced to adopt because no one series spans all the reactions described here.

The most striking difference between the milbemycins and the avermectins is the presence of a dioleandrose unit in position 13 of the avermectins, and it was tempting therefore to ascribe the higher anthelmintic potency of the avermectins to this disaccharide, as the other structural differences are relatively small. It was of interest therefore to prepare a series of 13 substituted milbemycin derivatives in order to examine their structure-activity relationships. The biological results of several 13 substituted milbemycins have already been described by the Merck group of Fischer, Mrozik, et al. (*9*). In this paper we will examine the synthesis and mechanism in some detail with emphasis on the biologically more important compounds.

Synthesis of intermediates.

We were able to functionalise the north-west corner of the molecule through epoxidation of the 9,10 double bond and subsequent opening of the epoxide to the allylic alcohol **7B**. Allylic rearrangement with Cr(VI) provided the 13β hydroxy milbemycin derivative **8B**, which was epimerised at C(13) to the 13α alcohol **10B** corresponding to ivermectin aglycone **5I** (*10*)(Fig. 1). Alternatively a direct microbiological hydroxylation of the milbemycins at the 13β position was accomplished (*11*). It is necessary for many of the reactions described hereafter to protect the 5-OH group. The choice of protecting group is not of primary concern, but we have found the $tBuMe_2Si$ (TBDMS) group to be consistently useful (*12*). Although only substructures are shown hereafter the protecting silyl group at position 5 should be understood to be present, except when explicitly otherwise indicated or when the biological activity is discussed.

Synthesis and mechanism of formation of 13-fluoro milbemycins.

The synthesis of 13β-fluoro-milbemycin D **10D** supplied us with mechanistic information, which later proved invaluable for the synthesis of other 13 substituted milbemycins. We treated the allyl alcohols **7D**, **8D**, and **9I** separately with Et_2NSF_3 (DAST)(*13*) at -60°C for 5 minutes (Fig. 2). From **7D** and **8D** the same 13β-fluoro product was formed, and from **9I** a mixture of 13β and 13α fluorides **10I** and **11I**.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

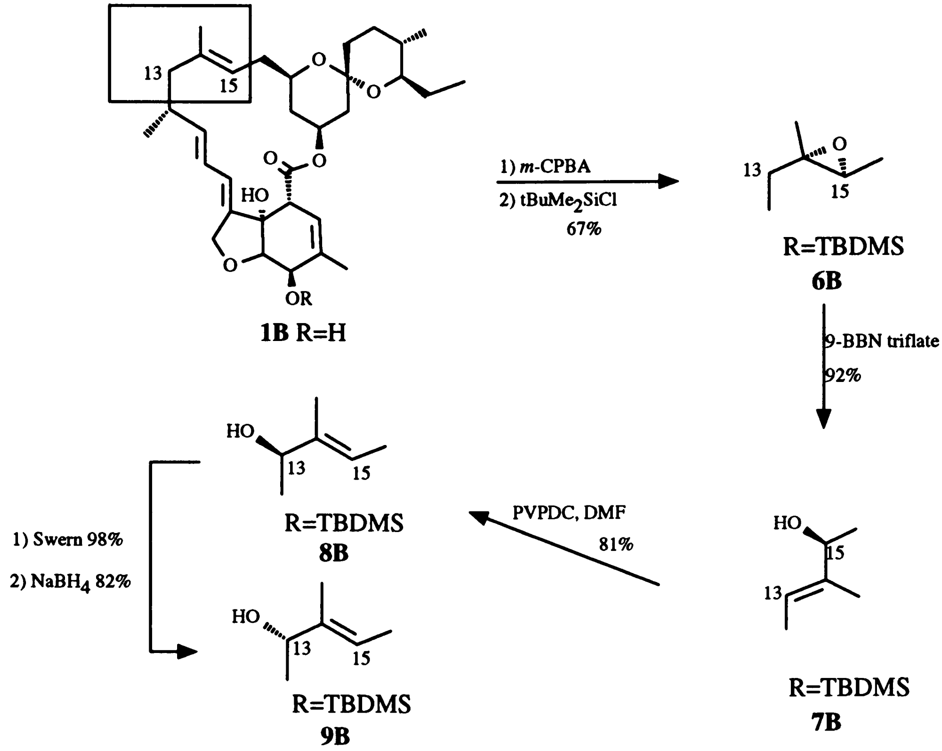
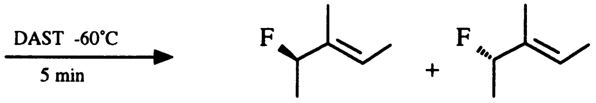

13
15
O
O
O
O
HO
O
OR
1B R=H
1) m-CPBA
2) tBuMe2SiCl
67%
13
O
15
R=TBDMS
6B
9-BBN triflate
92%
HO
15
13
R=TBDMS
7B
PVPDC, DMF
81%
HO
13
15
R=TBDMS
8B
1) Swern 98%
2) NaBH4 82%
HO
13
15
R=TBDMS
9B

Figure 1. Synthesis of intermediate allylic alcohols

7D,8D or **9I**



7D	**10D** (88%)	
8D	**10D** (100%)	
9I	**10I** (20%)	**11I** (49%)

Figure 2. Reactions of the three allylic alcohols with DAST

The reaction of allylic alcohols with DAST has been interpreted by Middleton as involving a cationic intermediate (*13*). Mixtures of products were formed, and there was a preponderence of 1,3 *syn* regioselectivity in less polar solvents. The clearest indication that the reactions described here have the same mechanism is the retention of stereochemistry observed at C(13) in **7D** → **10D**, **8D** → **10D** and **9I** → **11I**.

The inversion **9I** → **10I** is more ambiguous. An SN_2 mechanism has been suggested (*9*), however every attempt to induce an SN_2 reaction at positon 13 using a 13β leaving group was unsuccessful. For example treatment of the 13β-iodo derivative **15** with thiols or cuprate reagents did not lead to 13α-substituted products. As the same transition state is involved in an SN_2 reaction in the forward or reverse direction, we conclude that SN_2 reactions in both directions at C(13) are slow. Therefore we attribute the inversion **9I** → **11I** to an SN_1 reaction. All three reactions can thus be accomodated by one synthetic scheme involving the cation **12** (Fig. 3). It can be seen from these reactions, that of the four possible stereoisomers only the 13,14E 14,15E isomer **12** is formed.

Having established a common mechanism for all three reactions, it can be seen that an unusually stereo- and regioselective attack on an allylic cation takes place, which would be more indiscriminate in other structural surroundings. This regio- and stereoselectivity stems from the asymmetry of the cation **12**. The conformation of this cation is not amenable to study by molecular mechanics calculations. However a useful model is 13-keto-milbemycin A_4, which contains a similar array of planar sp^2 centres at the pertinent 13, 14, and 15 carbons, and exhibits a similar, but less pronounced, β-selectivity of nucleophilic attack at position 13 (*10*). Models (*10*) show that the α-face of the C(13), C(14), C(15) allylic system is sterically shielded at this position by the spiroacetal subunit, hindering attack at this face and inducing the observed stereoselectivity.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

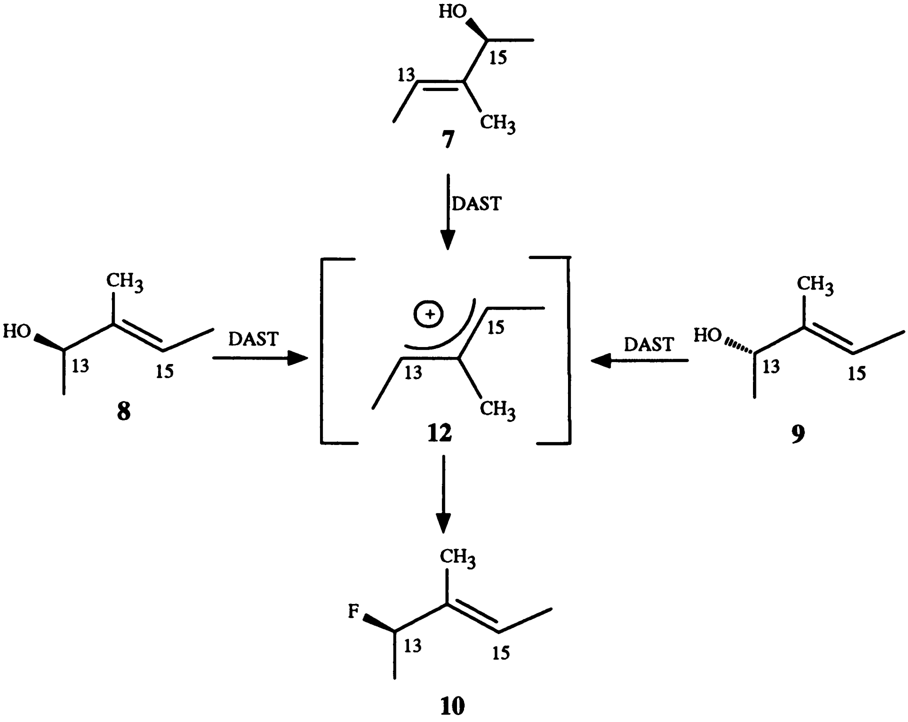


Figure 3. The DAST reactions involve a common cationic intermediate

The 13α-substituted fluoride **12I** is formed with retention of configuration (Fig. 2) in a manner typical for cations reacting with a nucleophile within a solvent cage (*14*). The starting aglycone **10I** has a propensity for reaction with retention, and it has been suggested that the cation formed from **10I** is stabilised through secondary orbital overlap with the 10,11 double bond in a conformation which allows nucleophilic attack only at the α-face (*9*). Although this proposal may well be correct, it is perhaps also interesting to consider this behaviour as one example of a more general phenomenon.

Unfunctionalised cycloalkyl bromides with ring sizes greater than 7 have greatly diminished SN_2 and greatly increased SN_1 reactivity in comparison with their open chain analogs (*15*). The data of Fierenz et. al. are shown below (Figure 4). The increased SN_1 reactivity has been convincingly explained by Prelog (*16*) and Brown (*17*), but the origin of the dependancy of SN_2 reactivity on ring size has never been explained. It seems clear, however, that the pentacoordinate transition state is not attainable for every conformation of a larger ring, and that substituted ring systems should be similarly affected. A further albeit negative indication of lowered SN_2 reactivity in macrolides is that in two reviews of the chemistry of macrolides (*18*), only one example of an SN_2 reaction is to be found (*19*). We suggest that lowered SN_2 reactivity is general for every macrolide including milbemycin, and consider the DAST reaction described here to be merely one example of this effect. Recognition of this effect will hopefully help chemists working with macrolides understand and plan their synthetic work.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

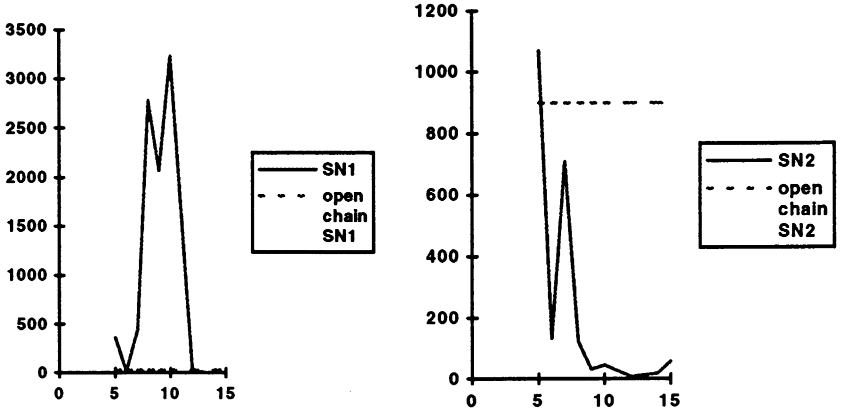
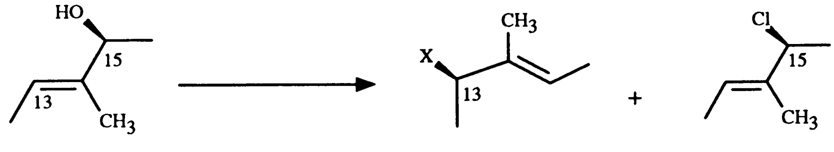


Figure 4. Reaction rates for SN1 and SN2 reactions plotted against ring size.

Synthesis of further 13β-substituted milbemycins.

As a consequence of the mechanistic origin of the observations described above, the SN_1 reaction at C(13) was successful, whereas the SN_2 did not take place under any conditions tried. The introduction of other groups into position 13 of the molecule would then be most sensibly achieved using an SN_1 strategy. In other words when the cation **12** is generated in the presence of other nucleophiles, stereoselective formation of 13β-substituted milbemycins can be expected, and, in fact, we were able to synthesise a large variety of compounds using this strategy.

Chlorination, bromination and iodination (*20*) of the allylic alcohols **7(A,B,** and/or **D)** led, in each case, to the 13β-substituted halides **13-15** (*21*)(Figure 5)(Table II). With phosphorus oxychloride, attack of chloride on cation **12** took place at position 15 in a side reaction to form **16D**, but again stereoselectively on the β face. The regioselectivity of the analogous alkylation reaction will be discussed in more detail below.



7

13-15

16D

Figure 5

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

Table II. Synthesis of 13β-halo-milbemycins

Substrate	Reagent	Product	X	Yield
7D	DAST, CH_2Cl_2, -60°	**8D**	F	97%
7D	$SOCl_2$, Et_3N, RT	**13D**	Cl	34%
7B	$SOCl_2$, Et_3N, RT	**13B**	Cl	47%
7A	$SOCl_2$, Et_3N, RT	**13A**	Cl	52%
7D	$POCl_3$, pyridine	**13D**[a]	Cl	28%
7D	PBr_3	**14D**	Br	49%
7D	PPh_3, I_2, imidazole	**15D**	I	64%

a) +**16D** (16%)

We applied many methods for generating the cation **12**. They were chosen case for case with regard to the nucleophile to be introduced, which is present in the reaction mixture before the cation is generated. Treatment of the allylic alcohols **7** or **8** with protic or Lewis acids is probably the most straightforward example. Conversion of the hydroxyl to a leaving group such as an ester or a sulfonate and subsequent treatment with a protic or Lewis acid is also often advantageous. Alternatively, for the synthesis of the 13 ketone (*10*), the 13β-bromide **14D** was treated with a silver salt.

As nucleophiles, several alcohols (*22*), thiols (*22*), acids (*23*), thioacids (*24*), amides (*23*), nitriles (*25*), and DMSO (*10*) were used successfully, with variable yields, again dependent on the method used. The products were often accompanied by the regioisomeric $\Delta^{13,14}$E-15S-substituted products analogous to **16D**, as expected from the allylic cation intermediate (Figure 6).

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

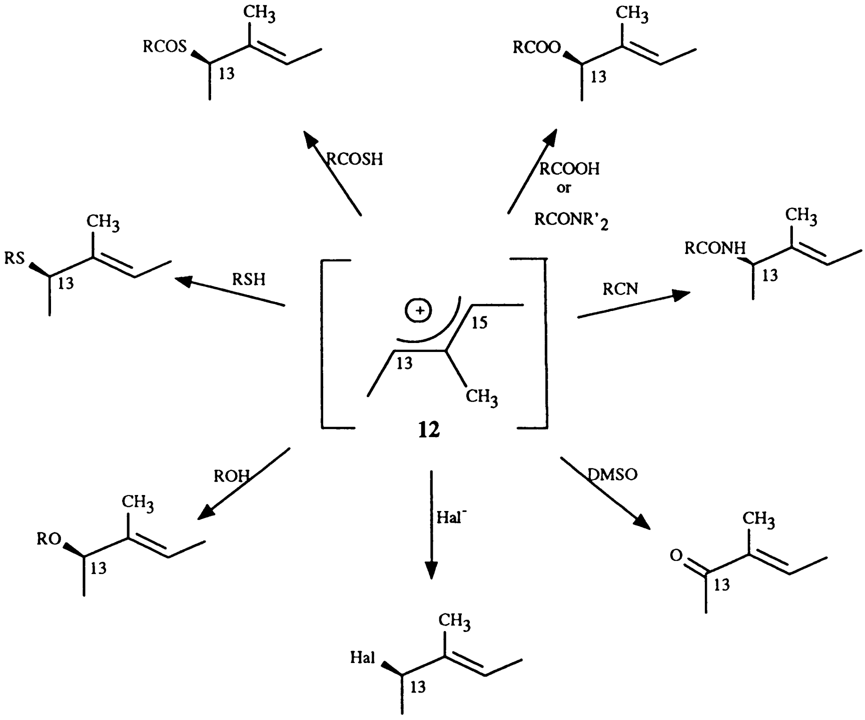


Figure 6. Synthesis of various 13β-substituted milbemycins.

Synthesis of 13β-alkyl milbemycins.

The synthesis of 13-alkyl substituted milbemycins proved to be a challenge. Many variants of the cuprate addition using several different leaving groups and different cuprate reagents (*26*) were unsuccessful. But by applying once more the by now already established strategy of using conditions which favour an SN_1 mechanism, we utilised the trialkylaluminium reaction of Yamamoto (*27*), which is known to occur *via* just this mechanism. Treatment of the allylic acetate **18B**, easily prepared from **7B**, with triethyl- or trimethylaluminium led to the desired 13β-alkyl milbemycins (**19B** and **20B**) contaminated in the former case by the $\Delta^{13,14}$E-15S-ethyl regioisomer **21B** (Figure 7).

American Chemical Society
Library
1155 16th St., N.W.
Washington, D.C. 20036

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

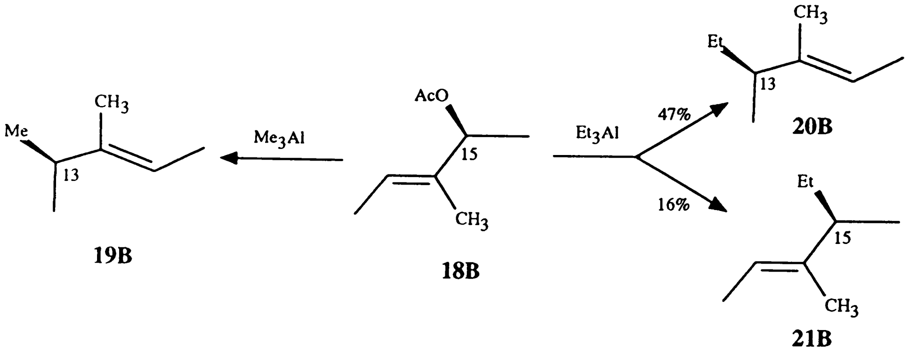


Figure 7. Synthesis of 13β-alkyl-milbemycins

13β-Ethyl-milbemycin A_4 **20B** was the most potent anthelmintic of the series of 13β-alkyl-milbemycins tested, and this compound was considered seriously for a time as a candidate for development. While the various data necessary for a full evaluation of the compound were being gathered, the process for the synthesis of 13β-ethyl milbemycin A_4 **20B** was optimised. The yield of the triethylaluminium reaction was good, and the route to the allylic ester starting material straightforward. The problem to be solved was clearly the lack of regioselectivity. The leaving group was varied (Figure 8), and the more pertinent results of these experiments are listed in Table III, from which some helpful conclusions can be drawn. Firstly, for carboxylic and sulfonate esters, the same 13:15 alkyl product mixture is obtained from either 13β- or 15S leaving groups (Entries 1 and 2; also 3 and 4). This is typical of the proposed cationic intermediate **12**. Secondly, bulky aluminate anions (R_3AlX^-) attack cation **12** preferentially at C(15). This is clear from the ratio of 13β-alkyl to 15S-alkyl product which decreases in the series $Me_3Al > Et_3Al > iBu_3Al$ to the point where the 15S-isobutyl compound becomes the major product. This bulkiness is met again in the aluminium sulfonate counterions to **12**, where the camphersulfonato-aluminate anion yields more 15S-ethyl than its mesylate analog (Entries 3 and 4). As always only attack on the β face of the cation **12** is observed. 15S-Chloro-Δ13,14-milbemycin A_4 **16B** produced, unexpectedly but to our satisfaction, the desired compound with high stereoselectivity in ca 50% yield (Entry 8).

The explanation for the regioselectivity of the reaction with the 15S-chloride requires a more detailed understanding of the mechanism of the reaction, which has much in common with the reaction of thionyl chloride with allyl alcohols (*28*).

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

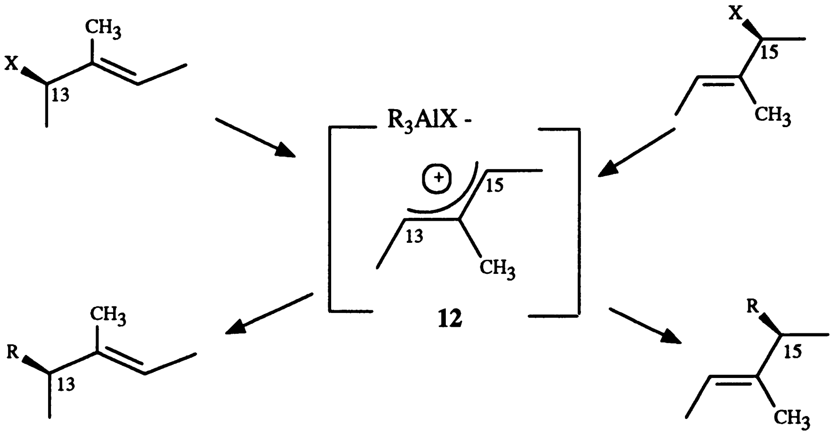
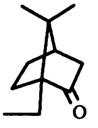
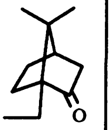


Figure 8

Table III. Regioselectivity of the alkylation

Entry	Starting Material	Reagent	Product Ratio 13:15
1	15-OAc	Et_3Al	75:25
2	13-OCHO	Et_3Al	75:25
3	$15\text{-}OSO_2Me$	Et_3Al	80:20
4	$13\text{-}OSO_2$ 	Et_3Al	30:70
5	$15\text{-}OSO_2$ 	Et_3Al	30:70
6	15-OAc	iBu_3Al	40:60
7	13-Cl	Et_3Al	70:30
8	15-Cl	Et_3Al	95:5

When allylic esters are used as substrates, the intermediate cation **12** is generated within a solvent cage. If the ion pair reacts before the two ions diffuse from the solvent cage, then retention of stereochemistry is observed. Should escape from the solvent cage be faster than product formation, then the reaction becomes unselective. In the present case the asymmetry of the milbemycin molecule induces a selectivity, irrespective of the mechanism of the reaction, so the results can be explained by both the caged or free ion pair mechanisms.

When allylic chloride **16B** is used as substrate (Table III; Entry 8), the reaction is ordered further. Restricted movement within the solvent cage influences profoundly the regioselectivity of the reaction. The trialkylaluminate anion derived from the allylic esters tumbles or rotates within the solvent cage. Both 13β-and 15S-leaving groups then give rise to the same distribution of anion rotamers, and consequently to the same distribution of regioisomers. However, rotation of the chloroaluminate anion is slower than product formation. The sequence of events begin with complexation of triethylaluminium with the chloride. Both partners are polarised by this complexation. The alkyl groups bound to aluminium now carry a small negative charge, and the terminal atom of the double bond in the allylic system a small positive one. These two moieties are aligned towards each other by a small electrostatic interaction, which increases after bond breakage and ion pair formation. Product formation occurs before the ion tumbles out of this alignment, and a 1,3-*syn* facial selectivity is observed. We may regard the reaction as pseudoconcerted. Gallina observed this behaviour on reaction of an allylic benzoate (*29*). However, in our case a 1:1 mixture of products was observed from the 15S-benzoate, and some substituted 15S-benzoates offered no improvement. We suggest that halides have a greater predisposition for pseudoconcertedness in comparison to esters or sulfonates, because of the ring size of the intermediate reacting complex (Figure 9). Six-membered rings are known to be less strained than 8-membered ones (*30*). The different product ratio obtained from the 13β-chloride is characteristic for non-rotating ion pairs (Table III; Entry 7), although full stereoselectivity was not observed.

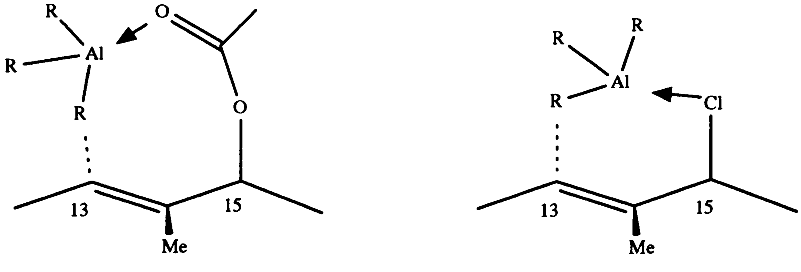
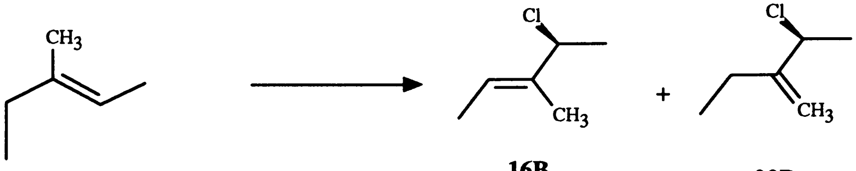


Figure 9. Pseudoconcerted trialkylaluminium reactions.

With the alkylation step now proceeding with an acceptable level of regioselectivity, the problem is now reduced to the synthesis of the intermediate allylic chloride **16B**. It was originally obtained only as a side product in the chlorination of **7B** with $POCl_3$ (Table II), but now a more selective method was required. The ene-like allylic chlorination of milbemycin with in situ generated HOCl has been shown by Burckhardt to produce exclusively the chloride **22B** with an exocyclic $\Delta^{14,29}$ double bond (*31*). In an attempt to direct double bond formation towards C(13), several other reagents were examined (*32*), many of which led to

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

mixtures of **16B** and **22B**. The most selective was tBuOCl (*33*), which yielded the endocyclic compound **16B** as the major product (see Fig. 10). More recently, A. Saito and colleagues at Sankyo (*34*) found that Me_3SiCl as an additive in this reaction improves the ratio of regioisomers to 8:1, from which the desired product **16B** was isolated in 63% yield.



16B **22B**

Reagent	Ratio **16B**:**22B**
$NaOCl/CO_2$	0:1
tBuOCl	3:2
tBuOCl ($+Me_3SiCl$)	8:1

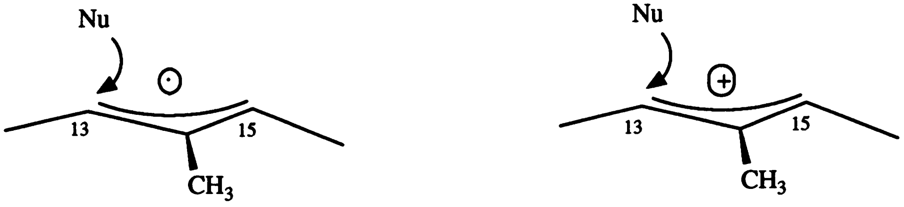
Figure 10. Regioselective chlorination

The critical steps in the reaction scheme now seem resolved. The regioselectivity of the chlorination and subsequent alkylation steps would be adequate for further development. However a further improvement was introduced, when it was found that the $tBuMe_2Si$ protecting group can be dispensed with, as both steps were sucessful with the unprotected 5-OH group. The hydroxy group reacts with triethylaluminium, but the aluminium-oxygen bond is cleaved again upon acidic work-up. The synthesis of 13β-ethyl-milbemycin A_4 **20B** from milbemycin A_4 **1B** is thus reduced to two steps with yields of 63% and 54% respectively.

Transition Metal Catalysed Synthesis.

Although the synthesis of 13β-ethyl-milbemycin A_4 **20B** was accomplished in a satisfactory manner with triethylaluminium, the synthesis of other analogs using this method in our laboratories was restricted to the series of commercially available trialkylaluminiums. In order to avoid the synthesis of these extremely air and moisture sensitive materials, and in the search for a new route to 13β-ethyl-milbemycin A_4 **20B**, a transition metal catalysed approach was explored. The well studied and understood palladium catalysed reactions used extensively by Trost and Tsuji (*35*) involve an SN_2 mechanism, which has been uniformly unsuccessful at the 13 position of milbemycin. However, allylic radicals have a planar structure similar to allylic cations. A milbemycin radical intermediate may be expected to have a similar degree of conformational freedom, and thus a similar stereoselectivity in its further transformations as the allylic cation **12**, which is a useful intermediate (see Figure 11). Consequently we counted on the propensity of transition metal catalysed reagents to undergo radical reactions (36) and were rewarded by some interesting new chemistry.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022


Nu
⊙
13
15
CH3
Nu
⊕
13
15
CH3

radical

cation 12

Figure 11. Radical *vs* cation as an intermediate

For the introduction of an alkyl group along these lines, an alkyl anion source and a transition metal salt or complex are necessary. Nickel was chosen as metal. The choice of alkyl anion source proved to be a matter of some importance, as demonstrated by the series of experiments depicted in Figure 12. Using the same nickel complex, the reaction took a very different course when either ethyl Grignard, ethylzinc bromide or diethylzinc was used as the ethyl source. In every case the intermediacy of the allylic radical may be assumed, which undergoes either Wurtz coupling or complexation with the nickel leading to the isolated products. No attempt will be made to explain these results, except to point out that no mechanism proposed in the literature for such alkyl-alkyl couplings (*37*) allows for such variability.

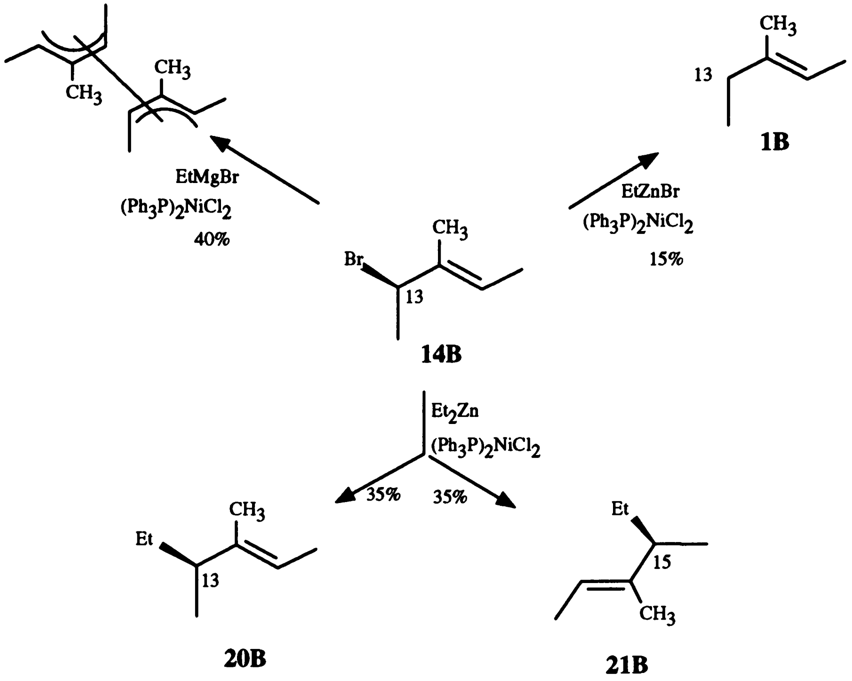
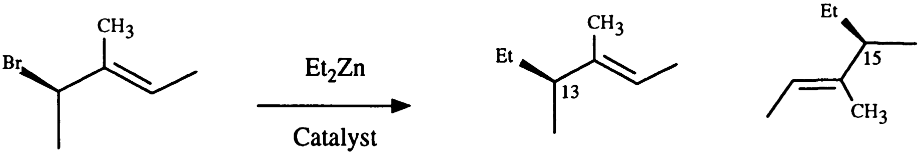

CH3
CH3
EtMgBr
(Ph3P)2NiCl2
40%
CH3
13
1B
EtZnBr
(Ph3P)2NiCl2
15%
CH3
Br
13
14B
Et2Zn
(Ph3P)2NiCl2
35%
35%
CH3
Et
13
20B
Et
15
CH3
21B

Figure 12. Dependence of product on ethyl anion source

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

The radical route is thus successful using diethylzinc, but again a mixture of 13β:15S regioisomers (**20B** and **21B**) was formed. A variety of other transition metal catalysts was screened using diethylzinc under conditions identical to those used above (Fig. 13 Table IV). Only nickel and cobalt complexes led to the desired products. The choice of ligand is important too. A typical result with many complexes was the formation of milbemycin dimers *via* Wurtz coupling. Palladium chloride complexed with bisdiphenylphosphinoferrocine (dppf) led to the formation of 5-OtBuMe$_2$Si-milbemycin A$_4$ together with its $\Delta^{13,14}$ isomer. However nickel dichloride complexed with 1,3-bisdiphenylphosphinopropane (dppp) or 1,4-bisdiphenylphosphinobutane (dppb) provided compounds **20B** and **21B** in good yields, again in approximately equal amounts. The best result was obtained with nickel chloride alone, without organic ligands, which led to a 2.5:1 ratio of the 13β:15S ethyl-milbemycin regioisomers, from which the desired isomer could be isolated in ca 40% yield.

A further improvement in this route was achieved with the discovery that the $\Delta^{13,14}$ 15S-chloro compound **16B** used for the alkyl aluminium reaction could also be used here. In addition the protection of the 5-hydroxy group could be dispensed with, although separation of the isomers was then more difficult. Overall from milbemycin A$_4$ **1B**, the synthesis then involved two steps of 63% and 40% yields respectively.



14B **20B** + **21B**

Figure 13.

Table IV. Optimisation of the Catalyst

Catalyst	Ratio **20B**:**21B**	Yield	Other Products
$(Ph_3P)_2NiCl_2$	1:1	70%	
dppe.$NiCl_2$			Slow Reaction
dppp.$NiCl_2$	1.7:1	50%	
dppb.$NiCl_2$	1:1	76%	
$(cyclohex_3P)_2NiCl_2$			Dimers
triphos.$NiClBF_4$			Dimers
dppf.$NiCl_2$			Slow Reaction
$(Ph_3P)_2CoBr_2$	1:1	40%	
dppf.$PdCl_2$			Reduction(13 and 15H)
$NiCl_2$	2.5:1	54%	

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

As a process for the synthesis of 13β-ethyl milbemycin A_4 **20B**, the nickel catalysed organozinc reaction is not competitive with the triethylaluminium reaction described above. However, it was possible to synthesise products, which would have been obtainable only with difficulty from the corresponding trialkylaluminium reagent (Fig. 14; Table V). Of course this new process has its own limitations. The most serious one is due to the tendency of organo transition metal compounds to undergo β-H elimination to the metal hydride. This results, in the present case, in the reduction of 15S-chloro-millbemycin A_4 **16B** or 13β-bromo-milbemycin A_4 **14B** to milbemycin A_4 **1B** when diisopropylzinc or di-3-phenylpropylzinc was used. Alkyl groups without hydrogens in the β position do not suffer from this problem, but use of dineopentylzinc and its phenyl analog resulted in a new β-elimination process, this time in the milbemycin ring affording a Δ12,13 milbemycin derivative, which was competitive with the alkyl-alkyl coupling. Diphenylzinc was unproblematic in this respect and produced smoothly 13β-phenyl-milbemycin A_4 **24B**.

This compound showed an interesting biological profile, and served as a lead for other 13β-aryl derivatives (*39*). Several were synthesised from the corresponding diarylzincs, which were prepared either in salt-free form using the centrifugation method of van Koten (*40*), or more often but with a decrease in yield, from reaction of the Grignard reagent with zinc chloride and coupling in situ.

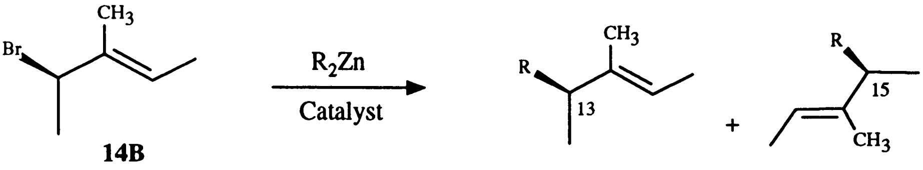
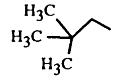
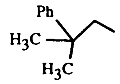
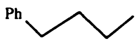


Figure 14.

Table V. Variation of the alkyl group

R Group	Ratio 13R:15R	Yield	Other Products
	**23B** 2:1	25%	$\Delta^{12,13}$ (3%)
			$\Delta^{12,13}$ (23%)
			13H(reduction) (65%)
iPr			13H(reduction) (35%)
Ph	**24B** 4:1	40%	

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

Biological Activity.

There are two ways of looking at the biological activity of this series of compounds. Firstly *in vivo* by measuring activity against a parasite isolated from, or in relation with, its host. Secondly *in vitro* by measuring the binding of the milbemycin analog to its receptor, which triggers a chain of physiological events which culminates in the death of the parasite. The receptor binding assay has been described by Schaeffer et.al.(*41*). Several 13-substituted milbemycin derivatives were tested in the receptor assay and all bound well to the receptor (*42*), however this was by no means reflected *in vivo*. Each molecule is a separate entity and is prone to the vagaries of the permeability of the various membranes and other bodily barriers, the metabolism in the host and parasite, and other factors, which are loosely termed transport phenomena. The transport factors dominate the *in vivo* results to such an extent that the tentative structure-activity relationships we made in the early stages of the work without the benefit of the results from the receptor tests were invalidated later by newer results.

Because the *in vivo* results did not correlate well with the *in vitro* results or the results of tests in model animals, we tested all new compounds for anthelmintic activity directly in a sheep test, involving a mixed infection of *Haemonchus contortus* and *Trichostrongulus colubriformis*.

Amblyomma hebraeum larvae on chicks were used as a test for tick activity. Mange activity was screened using a mouse model.

The anthelmintic activity of one of the first 13β-substituted milbemycins - 13β-fluoro-milbemycin D **10D** - was about the same as that of milbemycin D **1D** itself in the sheep test, but the activity against mange on mouse and *A.* ***hebraeum*** ticks on chicks was improved, which encouraged us to synthesise further 13β-substituted milbemycins.

Of the many compounds tested by us up to the synthesis of the 13-alkyl derivatives, the 13β-methyl- (**19**) and ethyl- (**20**) milbemycins showed very high activities in the sheep test described above. Whereas milbemycin A_4 **1B** does not control the mixed infection sufficiently at a dose of 0.2 mg/Kg, the 13β-ethyl derivative, brought about a 100% reduction of eggs/g feces at a dose of 0.025 mg/kg. The other parasites tested in sheep were controlled well by a dose of 0.1 mg/kg, and overall the compound appeared at least as useful as Ivermectin **4I** as an anthelmintic in sheep. Its disadvantages were firstly a weak activity against ectoparasites, and, more crucially for our purposes at the time, a weakness when used as an anthelmintic in cattle. One particularly critical example was a trial against *Ostertagia ostertagii* arrested larvae in cattle, normally controlled well by a dose of 0.2 mg/kg Ivermectin, which were not fully controlled by a dose of 0.5 mg/kg 13β-ethyl milbemycin A_4 **20B**. In the n-alkyl series, ethyl **20B** was slightly better than methyl **19B**, which in turn was much better than n-propyl. The longer straight chain 13β-alkyl milbemycins tested were virtually inactive in the sheep test.

13β-Neopentyl-milbemycin **23B** was a weak anthelmintic but was much more active than milbemycin A_4 **1B** against ectoparasites. Against *A.* ***hebraeum*** on chicks it was fully active at 0.5 mg/kg. In comparison milbemycin A_4 **1B** is inactive at 12 mg/kg, whereas ivermectin **4I** is fully active at 1.4 mg/kg. 13β-Phenyl-milbemycin A_4 **24B** shows both endo and ecto parasitic activity. It is similar in activity to 13β-ethyl-milbemycin A_4 **20B** against intestinal helminths both in sheep and cattle, again with about the same weakness against inhibited *Ostertagia* larvae in cattle. It is fully active against *A.* ***hebraeum*** in chicks at 1.5 mg/kg. However none of its analogs tested were substantially more active than 13β-phenyl-milbemycin A_4 **20B** itself.

Conclusion.

In summary we have shown how to functionalise the north-west corner of milbemycin and introduce various substituents into the 13 position. The consequences of using allylic cations and radicals as intermediates were evident in the mixtures of regioisomers which were formed in these reactions, and the problem posed by the regioisomeric mixture was solved in the case of 13β-ethyl-milbemycin A_4 **20B**, a potent sheep anthelmintic. Some interesting new organometallic chemistry was developed during this optimisation, which resulted in two two-step syntheses of 13β-ethyl-milbemycin A_4 **20B**.

The large differences in *in vivo* biological activity between structurally very similar compounds make the correlation of structure with activity precarious. After testing several 13β-substituted milbemycins in the receptor binding assay, we conclude that all 13β-substituted milbemycins are potentially active on the receptor. However due to the dominant effect of transport phenomena on the biological activity of the milbemycins, the testing of derivatives in vivo will always be important, with no rational way of avoiding the hard work involved in the synthesis and testing of a large number of derivatives, in order to find one with the required level and breadth of biological performance.

Literature Cited

1. Mishima, H.; Ide, J.; Muramatsu, S.; Ono, M. *J. Antibiot.* **1983**, *36*, 980.
2. Takiguchi, J.; Mishima, H.; Okusa, M.; Terao, M.; Aoki, A. Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120.
3. Blizzard, T.; Fisher, M. H.; Mrozik, H.; Shih, T. L. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G.; Ohno, M. Eds.; Springer Verlag: Berlin, 1990, pp 65-102.
4. Chabala, J. C.; Mrozik, H.; Tolman, R. L.; Eskola, P. Lusi, A.; Peterson, L. H.; Woods, M. F.; Fisher, M. H. *J. Med. Chem.* **1980**, *23*, 1134.
5. Davies, H. G.; Green, R. H. *Chem. Soc. Rev.* **1991**, *20*, 211-69.
6. Schaeffer, J. M. in *Ivermectin and Abamectin*; Campbell, W. C., Ed.; Springer-Verlag: New York, 1989; pp73-88.
7. Barden, P. C.; Ahmed, Z; Asato, G.; Buckwalter, B. L.; France, D.; Kameswaran, V.; Parker, E.; Tamura, S.; Tseng, S.-S. this volume.
8. Burckhardt, U., Eur. Pat. Appl. EP 165900; *Chem. Abstr.* **1986**, *105*, 37509. and Gehret, J.C., Eur. Pat. Appl. EP 237482; *Chem. Abstr.* **1989**, *110*, 134974.
9. Mrozik, H.; Linn, B. O.; Eskola, P.; Lusi, A.; Matzuk, A.; Preiser, F. A.; Ostlind, D. A.; Schaeffer, J. M.; Fisher, M. H. *J. Med. Chem.* **1989**, *32*, 375.
10. Frei, B.; Huxley, P.; Maienfisch, P.; Mereyala, H. B.; Rist, G.; O'Sullivan, A. C. *Helv. Chim. Acta.* **1990**, *73*, 1905.
11. Ramos Tombo, G. M.; Ghisalba, O.; Schär, H-P.; Frei, B.; Maienfisch, P.; O'Sullivan, A. *Agric. Biol. Chem.* **1989**, *53*, 1531. Nakagawa, K.; Miyakoshi, S.; Torikata, A.; Sato, K.; Tsukamoto, Y. *J. Antibiotics* **1991**, *44*, 232.
12. Greene, T. W.; Wuts, P. G. M. *Protective groups in Organic Chemistry*, 2nd ed.; Wiley: New York, 1991; p77.
13. Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
14. March, J. *Advanced Organic Chemistry*, 3rd Ed.; Wiley: New York, 1985; p287.
15. Schotsmans, L.; Fierenz, P. J. C.; Verlie, T. *Bull. Soc. Chim. Belg.* **1959**, *68*, 580-598.
16. Prelog, V. *Pure Appl. Chem.* **1963**, *6*, 545.
17. Brown, H.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

Downloaded by UNIV OF GUELPH LIBRARY on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch022

18. Kirst, H. A. in ref.3, pp 39-63. Omura, S. *Macrolide Antibiotics: Chemistry, Biology and Practice*; Academic Press: Orlando, Florida, 1984.
19. Hauske, J. R.; Guadliana, M.; Kostek, G. *J. Org. Chem. 1983, 48,* 5138.
20. Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Chem. Comm.* **1979**, 978.
21. Frei, B.; O'Sullivan, A. C.; Maienfisch. P., Eur. Pat. Appl. EP 180539; *Chem. Abstr.* **1987**, *106*, 4766j.
22. Frei, B.; O'Sullivan, A. C., Eur. Pat. Appl. EP 184173; *Chem. Abstr.* **1987**, *106*, 49886
23. Frei, B.; Mereyala, H. B.; O'Sullivan, A. C.; Sato, K.; Yanai, T., British Patent GB 2168345; *Chem. Abstr.* **1987**, *106*, 156159b
24. O'Sullivan, A. C.; Frei, B., Eur. Pat. Appl. EP 252879; *Chem. Abstr.* **1988**, *108*, 167207.
25. Kaboré, I. Z.; Khuong-Huu, F.; Pancrazi, A. *Tetrahedron* **1978**, *34*, 2815.
26. Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1989**, *54*, 2369.
27. Hashimoto, S.; Kitagawa,Y.; Iemura, S.; Yamamoto, H.; Nozaki, H. *Tet. Lett.* **1976**, *17*, 2615.
28. Ref.14; p289.
29. Gallina, C. *Tet. Lett.* **1985**, *26*, 519-22.
30. Ref. 14; p134.
31. Burckhardt, U., Eur. Pat. Appl. EP 143747; *Chem. Abstr.* **1986**,*104*, 109355.
32. De la Mare, P. B. D.; Bolton, R. *Electrophilic Addition to Unsaturated Systems,* 2nd Ed.; Elsevier: 1982; p113
33. Hertel, L. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1979**, *101*, 7620
34. Saito, A. Sankyo Ltd. Unpublished communication.
35. Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin; 1980.
36. Tsau, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547.
37. Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.
38. King, R. B.; Kapoor, P. N.; Kapoor, R. N. *Inorg. Chem.* **1971**, *10*, 1842.
39. O'Sullivan, A. C., Eur. Pat. Appl. EP 332580; *Chem. Abstr.* **1990**, *112*,138815.
40. van Koten, G. University of Utrecht, Holland. Personal communication.
41. Schaeffer, J. M.; Haines, H. W. *Biochem. Pharmacol.* **1989**, *38*, 2329.
42. Benson, J. A.; Bermudez, I.; Huxley, P.; Moser, P.; O'Sullivan, A. C. Ciba-Geigy Ltd. Manuscript in preparation.

RECEIVED July 5, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

Chapter 23

Highly Efficacious Non-ester Pyrethroid Insecticides with Low Toxicity to Fish

Gary A. Meier, Thomas G. Cullen, Saroj Sehgel, John F. Engel[1], Susan E. Burkart[2], Scott M. Sieburth[3], and Charles M. Langevine[2]

Agricultural Chemical Group, FMC Corporation, P.O. Box 8, Princeton, NJ 08543

Studies directed towards the discovery of insecticides with improved safety to fish have resulted in the identification of 2-cyclopropyl-2-arylethyl (3-phenoxyaryl)methyl ethers and thioethers. These non-ester pyrethroid analogs show potent activity as broad-spectrum insecticides and, in some cases, acaracides. In addition, these compounds are generally safe to fish and aquatic invertebrates. The chemistry and biological activity of these compounds will be discussed and compared to relevant commercial standards.

The pyrethroids possess a number of attributes that make them nearly ideal insecticides. Low mammalian toxicity, high intrinsic activity against a broad spectrum of insect pests, and generally low environmental mobility and persistence all contribute to the tremendous success of this class of chemistry. Pyrethroids, however, are usually quite toxic to fish. For example, cypermethrin has an LC_{50} of only 1 ppb vs. bluegills. This toxicity has limited the use of pyrethroid insecticides near aquatic environments and, until recently, has effectively excluded the pyrethroids from use in the paddy rice market. Clearly, development of a pyrethroid that retains the favorable characteristics of other pyrethroids while exhibiting reduced toxicity to fish would greatly expand the utility of this class of chemistry.

Studies have demonstrated that the ester linkage once thought to be necessary for pyrethroid activity can be replaced with certain bioisosteric groups without loss of insecticidal properties. For example, the ester linkage of fenvalerate (**1**) has been successfully replaced with an oxime ether to give compounds typified by (**2**) (*1*,*2*). The oxime ether (**2**) had an LC_{50} of 19 ppm vs. Southern armyworm in our testing, compared to fenvalerate's value of 40 ppm. The compounds MTI-500 (ethofenprox,

---

[1] Current address: Lithium Chemicals Division, FMC Corporation, P.O. Box 795, Highway 161, Bessemer City, NC 28016

[2] Current address: Agricultural Research Division, American Cyanamid Company, P.O. Box 400, Princeton, NJ 08540–0400

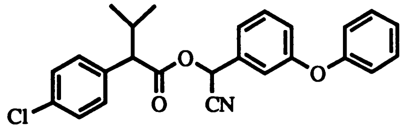
[3] Current address: Department of Chemistry, State University of New York at Stony Brook, Stony Brook, NY 11794

0097–6156/92/0504–0258$06.00/0

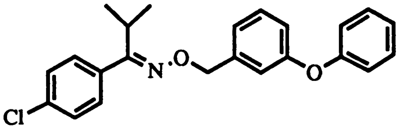
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

(3)) and MTI-800 (4) are further examples of successful bioisosteric replacement of the ester linkage, with Southern armyworm LC_{50} values of 16 and 7 ppm, respectively. These compounds also exhibit reduced toxicity to fish, with LD_{50}'s against carp of 5 ppm for ethofenprox and >40 ppm for MTI-800 (*3*).

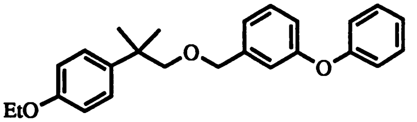
We wished to further explore the utility of ether and alkane bioisosteres in reducing the fish toxicity of pyrethroid insecticides. Elliott and Janes had previously reported that the cyclopropyl isostere of fenvalerate was less toxic than fenvalerate to rats and zebrafish (*4*). This observation lead us to propose structures generically represented by (5) as potential pyrethroid insecticides. The present chapter explores the structure-activity relationships of the ethers (Y = O) and thioethers (Y = S). The following chapter addresses the structure-activity relationships of the corresponding alkanes (Y = CH_2) (Cullen, T. G.; et al. in this volume).



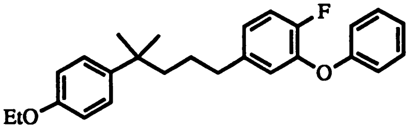
1



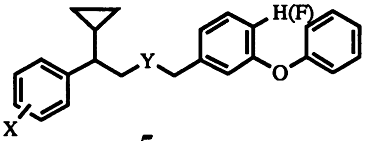
2



3



4

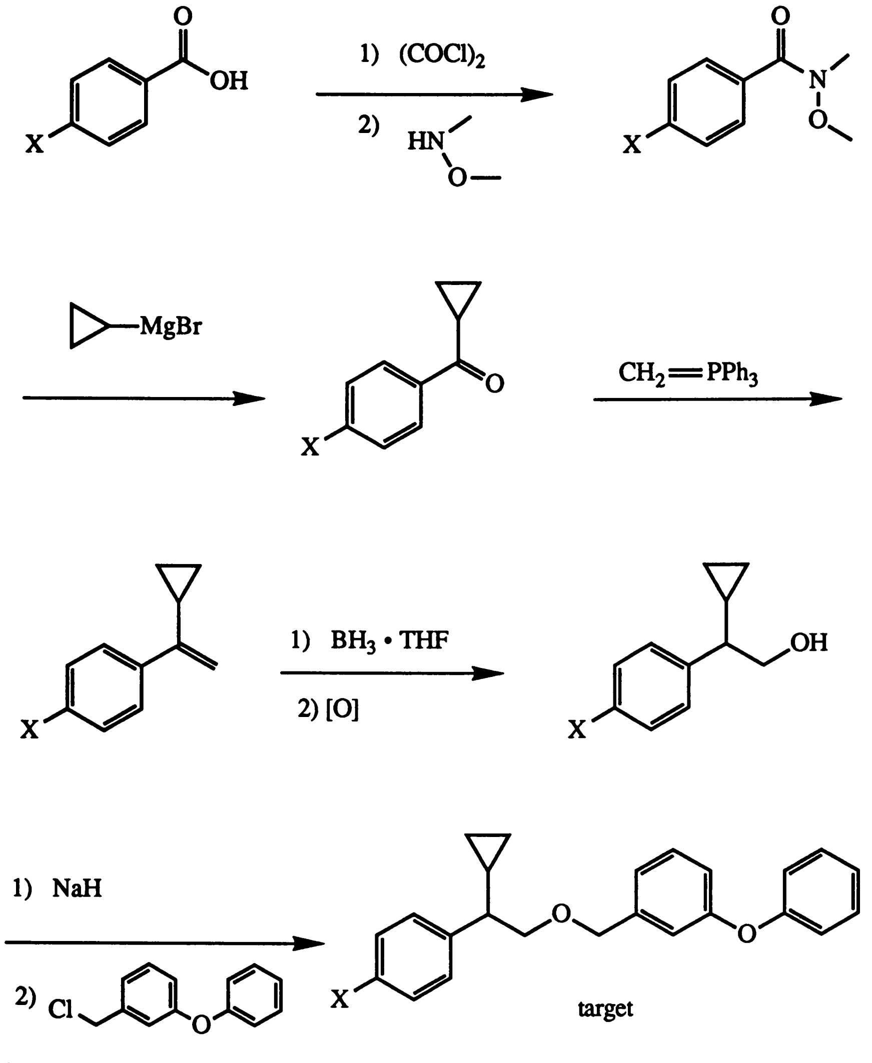


5

Synthesis Schemes

Racemic ether synthesis. The general synthesis scheme for the racemic ethers is shown in Scheme **1.** Synthesis details have previously been reported in greater detail, and will only be outlined here (*5*).

Treatment of the appropriately substituted carboxylic acid with oxalyl chloride in dichloromethane in the presence of a catalytic amount of DMF gave the acid chloride. This was added at 0° to N,O-dimethylhydroxylamine hydrochloride in THF containing two equivalents of pyridine to give the amide, typically in greater than 90% yield. Treatment of the amide with cyclopropyl magnesium bromide in THF gave the aryl cyclopropyl ketone in good yield. The methylene phosphorane was generated from methyltriphenylphosphonium bromide using NaH in DMSO. Addition of the ketone to the phosphorane gave the olefin in greater than 90% yield after workup. Addition of BH_3 -THF complex to the olefin stirring at 0° in dry THF gave 90 to 95% yield of the alcohol after standard oxidative quenching with methanol, aqueous NaOH, and hydrogen peroxide. The final step of the scheme, a Williamson ether synthesis, can be carried out either by deprotonating the alcohol with NaH in THF followed by addition of the appropriate benzyl halide, or under phase-transfer conditions, stirring the alcohol and benzyl halide neat in the presence of 5 mol % tetrabutylammonium bromide and 50% aqueous NaOH. These methods routinely produce yields of greater than 90%.

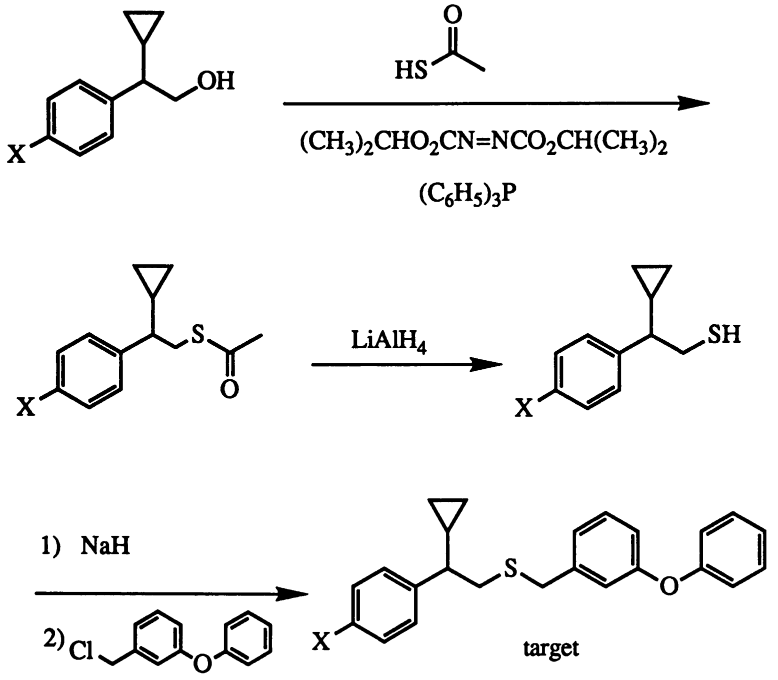


Scheme 1: Synthesis of Arylmethyl 2-Cyclopropyl-2-(aryl)ethyl Ethers

Thioether synthesis. Scheme 2. Triphenylphosphine was dissolved in THF and treated with one equivalent diisopropyl azodicarboxylate at 0°, warming gradually to room temperature. To this mixture, one equivalent thiolacetic acid and one-half equivalent of the 2-aryl-2-cyclopropyl ethanol intermediate prepared in Scheme 1 was added, yielding 80% of the desired thioester after workup and chromatography. The thioester was reduced with lithium aluminum hydride in THF to give the thiol in nearly quantitative yield. The thiol reacted under the Williamson conditions described above (NaH, THF) with the appropriate benzyl halide to give the thioether in 80% yield.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023



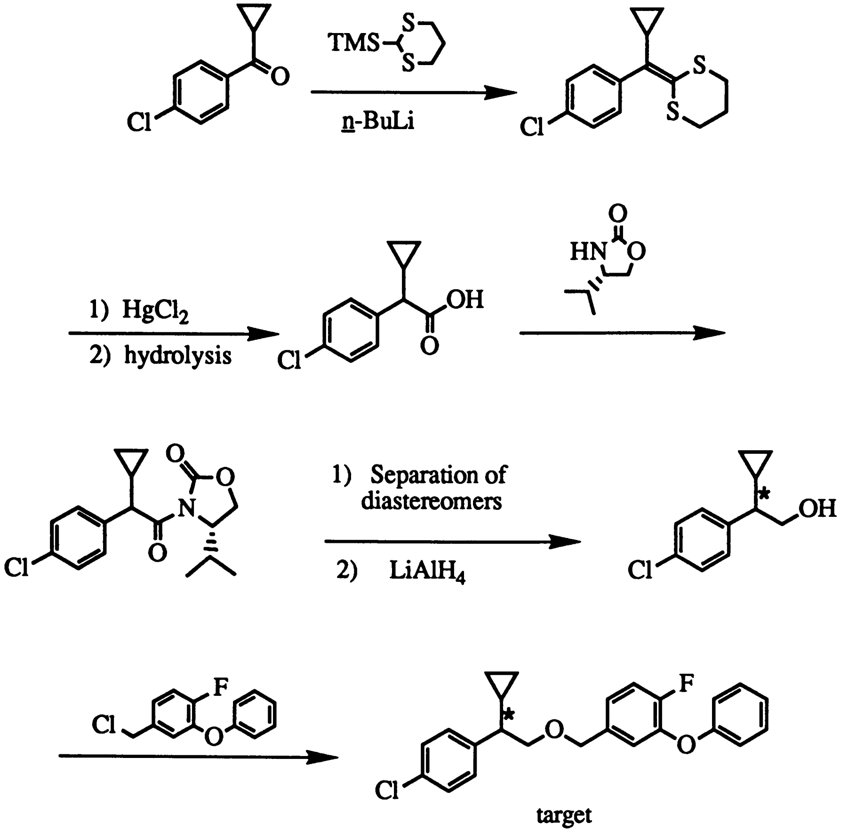
Scheme 2: Synthesis of Arylmethyl 2-Cyclopropyl-2-(aryl)ethyl Thioethers

Resolved ether synthesis. The resolved (4-fluoro-3-phenoxy)methyl 2-cyclopropyl-2-(4-chlorophenyl)ethyl ether was synthesized from 4-chlorophenyl cyclopropyl ketone as shown in Scheme 3. Deprotonating 2-trimethylsily-1,3-dithiane at 5° with n-BuLi in THF followed by addition of cyclopropyl 4-chlorophenyl ketone gave the tetrasubstituted alkene in nearly quantitative yield. Treatment with mercuric chloride in a refluxing solution of aqueous methanol yielded the methyl ester in modest yield. Hydrolysis of the ester with aqueous NaOH gave the carboxylic acid in greater than 90% yield. Conversion of the acid to the acid chloride using oxalyl chloride, followed by reaction with (4S)-(-)-4-isopropyl-2-oxazolidinone gave a diastereomeric mixture of amides, readily separable by silica gel chromatography. Isolated yield of the levorotatory diastereomer was 27%. Reduction of this material with $LiAlH_4$ in THF at 0° gave the resolved alcohol in 88% yield. Reacting a small sample of the alcohol with the acid chloride derived from (R)-(+)-α–methoxy-α–trifluoromethyl)phenylacetic acid (Mosher's acid) gave the corresponding (α-methoxy-α-trifluoromethyl)phenylacetic ester. 19F NMR analysis of the trifluoromethyl signal showed the alcohol to have an enantiomeric excess of > 90%. Reacting the resolved alcohol with 4-fluoro-3-phenoxyphenyl benzyl chloride under Williamson conditions gave the resolved ether in 75% yield, $[\alpha]_D = -23.62°$.

Biological Testing

The compounds were screened for insecticidal and acaricidal activity against the following species: cabbage looper (*Trichoplusia ni*), southern armyworm (*Spodoptera*

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023



Scheme 3: Synthesis of Resolved Arylmethyl 2-Cyclopropyl-2-(aryl)ethyl Ethers

eridania), tobacco budworm (*Heliothis virescens*), Mexican bean beetle (*Epilachna varivestis*), pea aphid (*Acyrthosiphon pisum*), potato leafhopper (*Empoasca fabae*), brown planthopper (*Nilaparvata lugeus*), and twospotted spider mite (*Tetranychus urticae*).

The activity of the test compounds against cabbage looper, tobacco budworm and Mexican bean beetle was determined by spraying the upper and lower surfaces of the leaves of pinto bean plants with test solution until run-off and infesting with second instar larvae after the foliage had dried (ten larvae for each of two replicates for each compound). The test solutions were prepared by appropriate dilution from a stock solution of experimental compound in 10% acetone/water.

The activity against pea aphid was determined in similar fashion, except that fava bean plants were used and the leaves were infested with adult aphids.

The activity against potato leafhopper was determined in a similar fashion except that the treated fava bean plants were removed from their pots by cutting the stem just above the soil line. The excised leaves and stems were placed in petri plates and infested with two-to-three-day-old potato leafhopper adults.

The activity against mites was determined on pinto bean plants. The bean leaves were pre-infested with adult mites (about 75 mites for each of two replicates for each compound), then sprayed until run-off with test solution.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

To prevent escape of the insects from the test site, the treated plant or excised leaves were placed in capped cups or other appropriate containers. The tests were transferred to a holding room at 25°C and 50% relative humidity for an exposure period of 48 hours. At the end of the exposure period, percent mortality was determined and LC_{50} values were determined by probit analysis.

The activity against brown planthopper was determined using TN1 rice plants that were 35-50 days old. The plants were trimmed to 1.0 feet and to contain four tillers. The plants were sprayed to run-off and allowed to dry. Twenty brown planthopper nymphs (2nd-3rd instar) were introduced per pot and covered with a mylar cage. Mortality readings were taken 24 hours after infestation; the LC_{50} values were determined by probit analysis.

Efficacy in residual testing was determined by spraying the test plants to run-off with aqueous dilutions of the compounds. The treated plants were held under greenhouse conditions for the appropriate period of time before infestation with insects. The test was then completed as described for the initial evaluations.

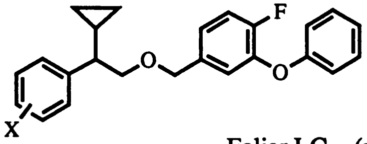
The fish toxicity was determined by testing against fathead minnows (*Pimephales promelas*) and bluegill (*Lepomis macrochirus*). Fish testing required the test materials to be prepared as acetone (1%)/water solutions diluted to the appropriate volume and allowed to equilibrate for five to six hours in one-quart Mason jars before being infested with three minnows or bluegills (25-35 mm). Mortality counts were taken 24 hours after infestation.

Testing for toxicity to water flea (*Daphnia magna*) was performed by the I.T. Corporation Laboratories. Test compound dilutions were prepared in water/acetone to a final acetone concentration of 0.1 mL/L. Two replicates of ten *Daphnia*/replicate were run at each concentration, ranging from 7.6 to 9.5 x 10^{-4} mg/L. Mortality was recorded after 48 hours. Water-quality parameters, such as temperature, pH and dissolved oxygen were monitored and remained within acceptable limits for the duration of the test.

Results and Discussion

An abbreviated chlorine probe set was synthesized on the phenyl ring of the 2-phenethyl moiety to determine which position(s) were most sensitive to substitution. The results are shown in Table I, for a series of analogs employing 4-fluoro-3-phenoxyphenyl as the pyrethroid alcohol fragment. Substitution in the 4-position of the phenyl ring gave rise to the most active compounds against most foliar feeding pests, with the

Table I: Effects of Varying the Substitution Position on the Phenethyl Phenyl Ring



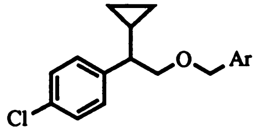
X	Foliar LC_{50} (ppm) Cabbage Looper	Mexican Bean Beetle
4-chloro	1	4
3-chloro	17	6
2-chloro	250	36
3,4-dichloro	11	1

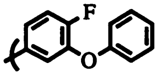
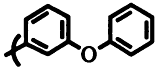
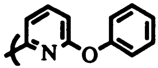
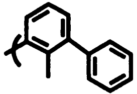
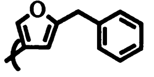
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

3-substituted and 3,4-disubstituted compounds slightly less active. Substitution in the 2-position greatly reduced the activity of compounds in this class. The 4-position was selected for further optimization.

A series of compounds to determine the most effective pyrethroid alcohol fragment was next synthesized. The results are shown in Table II. The 4-fluoro-3-phenoxyphenyl group gave rise to the best foliar activity. The 3-phenoxyphenyl and 6-phenoxy-2-pyridyl groups were also quite active, though significantly less so than the 4-fluoro-3-phenoxyphenyl group. The 2-methyl[1,1'-biphenyl]-3-yl and 2-benzyl-4-furanyl (Elliott's alcohol) groups showed only modest activity.

Table II: Pyrethroid Alcohol Selection



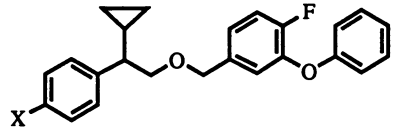
Ar	Foliar LC_{50} (ppm)	
	Cabbage Looper	Mexican Bean Beetle
	1	4
	15	9
	13	23
	91	49
	69	100

After the most effective pyrethroid alcohol fragment was identified, a series of compounds were made in which the substituent on the 4-position of the phenethyl phenyl ring was varied. Table III shows the results. The 4-chloro substituent was the best of this series, giving rise to a compound essentially as active as cypermethrin. Other halogen substituents or an ethoxy substituent were also fairly good. All of the compounds in this set were significantly more active than ethofenprox against Mexican bean beetle, and with the exception of the t-butyl substituent, all were significantly more active than ethofenprox against cabbage looper as well.

Comparisons of ether vs. thioether bioactivity are shown in Table IV for both the 4-fluoro-3-phenoxyphenyl and the 3-phenoxyphenyl analogs. The ethers were more active in both cases, although the thioethers were still significantly more active than ethofenprox, at least in the 4-fluoro-3-phenoxyphenyl series.

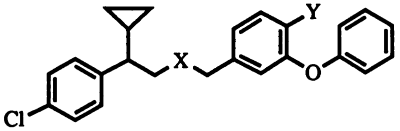
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

Table III: Effects of Varying the 4-Substituent on the Phenethyl Phenyl Ring



X	Foliar LC_{50} (ppm)	
	Cabbage Looper	Mexican Bean Beetle
Cl	1	4
CH_3CH_2O	5	11
Br	7	19
F	13	15
CH_3	35	3
H	40	19
$(CH_3)_3C$	100	3
ethofenprox	91	37
cypermethrin	2	1

Table IV Ether vs. Thioether Comparison

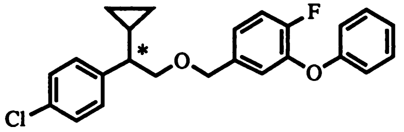


X	Y	Foliar LC_{50} (ppm)	
		Cabbage Looper	Mexican Bean Beetle
S	F	10	11
O	F	1	4
S	H	24	45
O	H	16	9
ethofenprox		91	37

Both enantiomers of 2-cyclopropyl-2-(4-chlorophenyl)ethyl (4-fluoro-3-phenoxyphenyl) methyl ether were synthesized using the procedure shown in Scheme 3. The absolute stereochemistry has not been assigned, but both enantiomers were tested against several insect species as shown in Table V. The racemic material was the biologically active species, with approximately twice the insecticidal activity of the racemic material. The (+)-enantiomer did have some insecticidal activity, but the material tested was contaminated with as much as 5% of the (-)-enantiomer. This contamination was believed to be responsible for all or most of the insecticidal activity of the (+)-enantiomer.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

Table V: Bioactivity of Resolved Enantiomers



	Foliar LC_{50} (ppm)	
Species	(+)-enantiomer	(-)-enantiomer
Cabbage Looper	5	1
Mexican Bean Beetle	49	2
Southern Armyworm	22	2
Pea Aphid	59	6

The compounds described to this point exhibit good activity against lepidopteran and coleopteran species, but very low activity against mites and aphids. Upon further exploration of the Structure-Activity Relationships at the 4-position of the phenethyl phenyl ring, however, we were lead into a set of compounds which had excellent activity against mites, and in some cases, aphids. The substituents which gave rise to mite activity all contained the trifluoromethyl group, with the interesting exception of the cyclopropylmethoxy substituent. Table VI shows the bioactivity for the 4-fluoro-3-phenoxyphenyl analogs in this series.

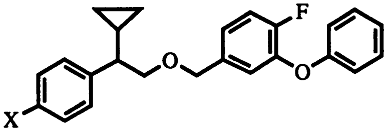
Based on these results, several analogs of the 4-Cl, 4-CF_3 and 4-CF_3O compounds were selected for further testing. Foliar test data on potato leafhopper and brown planthopper for these compounds and for ethofenprox are given in Table VII, which also includes field test data on several pests of economic importance. The 3-day and 7-day residual activity (greenhouse) for several analogs is shown in Table VIII and compared to that of ethofenprox.

Table IX shows the mammalian toxicity data (mouse acute oral and guinea pig acute dermal LD_{50} values) for several of these compounds. All compounds tested showed a negative response in the Ames Assay.

Finally, Table X shows aquatic safety data for several compounds tested in static systems on bluegill (*Lepomis macrochirus*) and on water fleas (*Daphnia magna*). Data for ethofenprox and cypermethrin are included. Ethofenprox is used commercially on paddy grown rice, and so was chosen as a suitable commercial standard for aquatic safety comparisons.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

Table VI: Bioactivity of Mite-Active Compounds



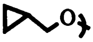
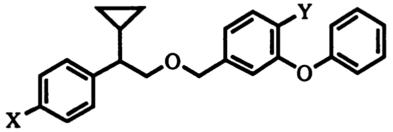
	Foliar LC_{50} (ppm)			
X	Cabbage Looper	Mexican Bean Beetle	Pea Aphid	Twospotted Spider Mite
CF_3O	0.6	0.2	0.6	1
CF_3	2	1	5	13
CF_3S	14	1	~200	1
$CF_3S(O)$	23	26	~250	2
$CF_3S(O)_2$	19	9	110	3
	2	41	~400	7
ethofenprox	91	37	210	480
cypermethrin	2	1	30	170

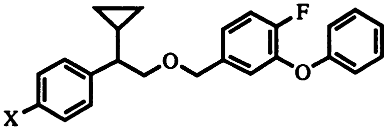
Table VII: Additional Biodata



		Foliar LC_{50} (greenhouse test) or Effective Use Rate (field test)	
X	Y	Pest Species	Bioactivity
CF_3O	F	Potato Leafhopper	$LC_{50} < 1$ ppm
		Brown Planthopper	$LC_{50} = 5$ ppm
		Tobacco Budworm (field test)	0.025 lbs a.i./acre
CF_3O	H	Potato Leafhopper	$LC_{50} = 3$ ppm
		Brown Planthopper	$LC_{50} = 6$ ppm
		Tobacco Budworm (field test)	0.025 lbs a.i./acre
		Gypsy Moth (field test)	< 0.025 lbs a.i./acre
Cl	F	Potato Leafhopper	$LC_{50} = 7$ ppm
		Brown Planthopper	$LC_{50} = 16$ ppm
		Green Leafhopper (field test)	0.15 lbs a.i./acre
ethofenprox		Potato Leafhopper	$LC_{50} = 8$ ppm
		Brown Planthopper	$LC_{50} < 5$ ppm
		Tobacco Budworm (field test)	0.15 lbs a.i./acre

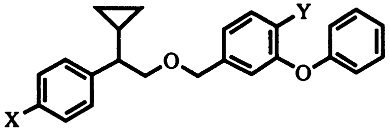
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

Table VIII: Residual Activity of Selected Analogs



X	Cabbage Looper Foliar LC_{50} (ppm) Initial Activity	3-Day Residual	7-Day Residual
CF_3O	0.5	~2	>8
CF_3	2	<8	<8
Cl	1	20	25
ethofenprox	91	300	>500

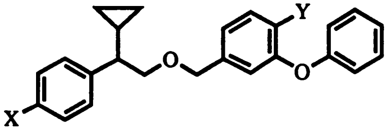
Table IX: Mammalian Toxicity Data



X	Y	Acute LD_{50} (ppm) Oral (mouse)	Dermal (Guinea pig)
CF3O	F	~ 50	not tested
CF3O	H	> 50	not tested
Cl	F	> 50	> 300
Cl	H	> 50	> 300

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

Table X: Aquatic Testing Data



		Vertebrate Toxicity	Invertebrate Toxicity
X	Y	Bluegill % kill (rate)	Water flea LD_{50}
CF_3	H	not tested	< 1 ppm
Cl	F	50% (3 ppm)	not tested
Cl	H	83% (3 ppm)	4 ppm
ethofenprox		83% (6 ppm)	< 1 ppm
cypermethrin		50% (0.001 ppm)	2 ppm

Conclusions

The non-ester pyrethroids described here are potent, broad-spectrum insecticides, and compared to typical ester pyrethroids, are generally quite safe to fish and, in some cases, to aquatic invertebrates. The most active compounds described here are considerably more active than the commercial rice insecticide ethofenprox on the species in our screen, and several are equivalent or superior to cypermethrin. The limited field test data reported here supports the conclusion that these compounds have commercial-level activity.

The 4-fluoro-3-phenoxybenzyl moiety is the most effective pyrethroid alcohol equivalent in this series. The ethers analogs are more active against insect pests than the thioethers. Configuration at the molecule's one chiral center is important; the resolved enantiomers of 2-cyclopropyl-2-(4-chlorophenyl)ethyl (4-fluoro-3-phenoxyphenyl)methyl ether demonstrated that the levorotatory isomer was approximately twice as active as the racemic material. Substitution at the 4-position of the phenethyl phenyl ring was most important for biological activity. The compounds tolerated a variety of substituents in this position; however introduction of CF_3 or CF_3O not only boosted the compound's activity against lepidopteran and coleopteran species, but also gave rise to potent activity against mites and aphids.

Acknowledgments

The authors would like to thank Larry Marek and George Meindl for carrying out the insect bioevaluations at FMC, as well as E.D. Magallona for the testing he carried out against rice pests in the Philippines. Annette Slaney conducted most of the fish toxicity testing. Finally, the authors acknowledge the support of FMC Corporation.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch023

Literature Cited

1. Holan, G.; Johnson, W. M. P.; O'Keefe, D. F.; Quin, G. L.; Rihs, K; Spurling, T. H.; Wolser, R.; Virgona, C. T.; Frelin, C.; Lazdunski, M.; Johnston, G. A. R.; ChenChow, So. *Recent Advances in the Chemistry of Insect Control*, James, N. F., Ed.; The Royal Society of Chemistry: London, **1985**; pp 114-132.
2. Cullen, T. G.; Manly, C. J.; Cruickshank, P. A.; Kellar, S. M. *Synthesis and Chemistry of Agrochemicals*; Baker, D. R.; Fenyes, J. G.; Moberg, W. K.; Cross, B., Eds.; American Chemical Society: Washington, D.C., **1987**; pp 173-188.
3. Udagawa, T.; Numata, S.; Oda, K.; Shiraishi, S.; Kodaka, K.; Nakatani, K. *Recent Advances in the Chemistry of Insect Control*, James, N.F. Ed.; The Royal Society of Chemistry: London, **1985**; pp 192-204.
4. Elliott, M.; Janes, N. F. *Advances in Pesticide Science* , Part 2, Geissbuhler, H. Ed.; Pergamon Press: New York, **1979**; pp 166-173.
5. Meier, G. A.; Sieburth, S. M.; Cullen, T. G.; Engel, J. F., U.S. Patent 4,808,762, **1989**.

RECEIVED July 6, 1992

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

Chapter 24

1,4-Diaryl-1-cyclopropylbutanes

Highly Efficacious Insecticides with Low Fish Toxicity

**Thomas G. Cullen, Scott M. Sieburth[1], John F. Engel[2], Gary A. Meier,
Albert C. Lew[3], Susan E. Burkart[3], Francis L. Marek,
and James H. Strickland[4]**

**Agricultural Chemical Group, FMC Corporation, P.O. Box 8,
Princeton, NJ 08543**

1,4-Diaryl-1-cyclopropylbutanes are potent broad spectrum foliar insecticides and, in some cases, acaricides. These highly lipophilic non-ester pyrethroids are relatively safe to fish as well as mammals. The cyclopropyl group is found to be essential; replacement by an isopropyl group results in a dramatic loss in activity. The insecticidal activity, fish safety and mammalian safety are equivalent to relevant standards.

A goal of our research program was to develop an insecticide that had foliar activity against cotton pests (e.g., worms) and rice pests (e.g., hoppers). In addition, we set the criteria that our compounds possess fish and mammalian safety minimally equivalent to ethofenprox, **1**, and MTI-800, **2**. The structures of the compounds referred to in this chapter are in Figure 1.

One part of that program was the preparation of 1-cyclopropyl-1-(4-substituted phenyl)-4-(4-fluoro-3-phenoxyphenyl)butane, **3**. In that instance, we replaced the ester linkage of fenvalerate, **4**, by an ethylene linkage. Furthermore, the isopropyl group of fenvalerate was replaced by the isosteric cyclopropyl group. In our case, this was found to lead to increased insecticidal activity. Compounds in which the cyano group of fenvalerate is retained will be discussed at a future date. These changes resulted in compounds in which the insecticidal activity was maintained (*1, 2*). It is well known that replacement of the carboxyl group in fenvalerate by an oxime ether linkage maintains insecticidal activity (*3, 4.*). Yet not all replacements of the ester linkage were successful. An amide or a thioester linkage

---

[1] Current address: Department of Chemistry, State Universty of New York at Stony Brook, Stony Brook, NY 11794

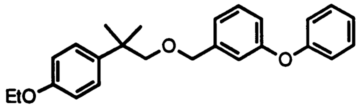
[2] Current address: Lithium Chemicals Division, FMC Corporation, P.O. Box 795, Highway 161, Bessemer City, NC 28016

[3] Current address: Agricultural Research Division, American Cyanamid Company, P.O. Box 400, Princeton, NJ 08540–0400

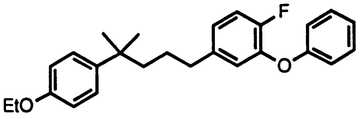
[4] Current address: Van De Mark Chemical Company Inc., 1 North Transit Street, Lockport, NY 14094

0097–6156/92/0504–0271$06.00/0

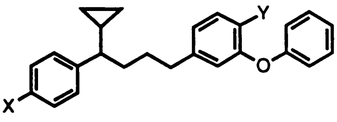
Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024



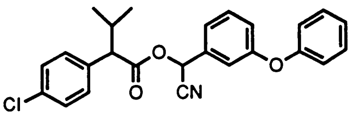
1
ethofenprox



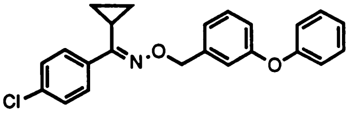
2
MTI-800



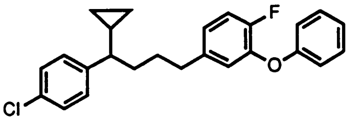
3 (Y = H or F)



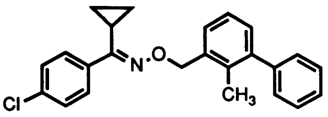
4
fenvalerate



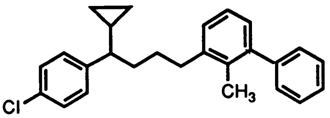
5



6



13

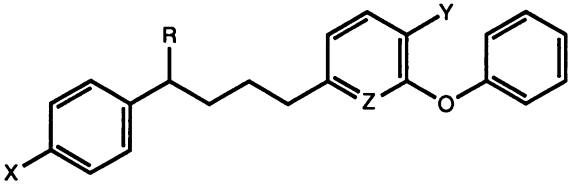


14

Figure 1. Structures of Compounds Discussed

shows diminished biological activity (*5*). Enhanced fish safety as well as good insecticidal activity is shown when the ester group is replaced with an ether linkage and the isopropyl group is replaced by a dimethyl group, resulting in ethofenprox, (*6*) Furthermore, replacement of the ether linkage by an alkylene linkage results in MTI-800 that is more active than ethofenprox and safer to fish (*7*). The transformation from ethofenprox to MTI-800 also included the addition of a 4-fluoro group. That change can contribute significantly to increased insecticidal activity, but the effect on safety to fish is not known by us.

For our purposes, Figure 2 represents those portions of the 1,4-diaryl-1-cyclopropylbutanes that were examined for their effect on biological activity and that will be covered in this chapter. One of our interests was to determine whether the cyclopropyl group is essential for good foliar activity. Our work in the alkyl aryl oxime ether area has shown that cyclopropyl and isopropyl groups are both active in foliar testing (*5*). We predicted that when Y is equal to fluorine this would be more active than the hydrogen compounds. This is the case in a direct analogy to the pyrethroid esters.



R = cyclopropyl, isopropyl, normal propyl
Y = hydrogen or fluorine
Z = carbon or nitrogen
X = Cl, CF_3, OC_2H_5, OCF_3

Figure 2. Structure Changes

Synthesis

The original synthesis employed for the preparation of 1-(4-chlorophenyl)-1-cyclopropyl-4-(3-phenoxyphenyl)butane (*6*) is shown in Figure 3. This scheme starts with 3-phenoxybenzaldehyde which is treated with commercially available ethoxycarboxylmethylene triphenylphosphorane in one portion to give ethyl 3-(3-phenoxyphenyl)acrylate in 75% yield. This material is reduced to 3-(3-phenoxyphenyl)propanol in 90% using lithium aluminum hydride, and converted to the corresponding 3-(3-phenoxyphenyl)propyl bromide in 70% yield using phosphorus tribromide. Refluxing this bromide and triphenylphosphine in acetonitrile gave the desired 3-(3-phenoxyphenyl) propyltriphenylphosphonium bromide, **7**. Under a nitrogen atmosphere, compound **7** is treated with n-butyl lithium, followed by 4-chlorophenyl cyclopropyl ketone, **8**, to give 1-(4-chlorophenyl)-1-cyclopropyl-4-(3-phenoxyphenyl)-1-butene, **9**, in 45% yield. Compound **9** is reduced to **6** in 90% yield using hydrogen with Raney nickel as the catalyst. This is found to be the catalyst of choice for this hydrogenation as other catalysts such as platinum or palladium open the cyclopropane ring to give the n-propyl derivative as well as reducing the double bond.

We desired a more efficient synthesis of **6**. Figure 3 required two Wittig reactions, a lithium aluminum hydride reduction and a bromination with phosphorus

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

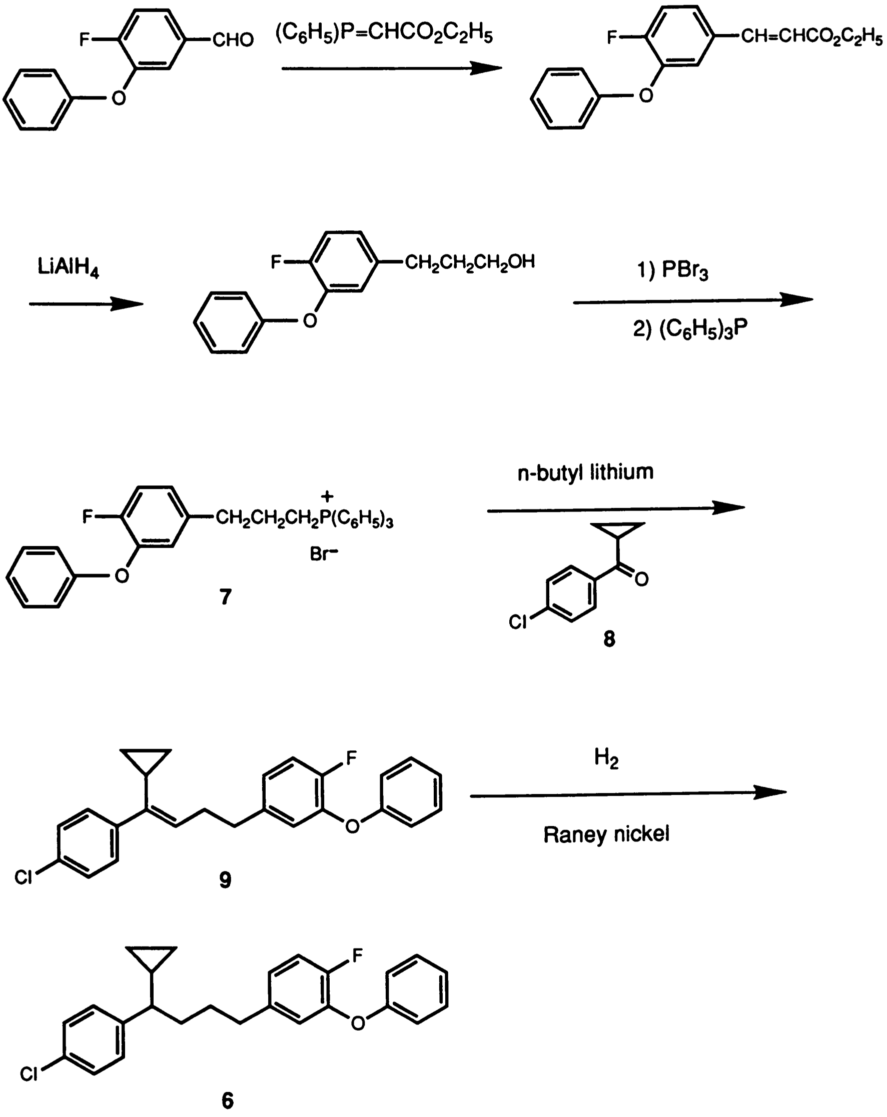

F
CHO
O
(C6H5)P=CHCO2C2H5
F
CH=CHCO2C2H5
O
LiAlH4
F
CH2CH2CH2OH
O
1) PBr3
2) (C6H5)3P
F
+
CH2CH2CH2P(C6H5)3
Br−
O
7
n-butyl lithium
O
Cl
8
F
O
Cl
9
H2
Raney nickel
F
O
Cl
6

Figure 3. Synthesis of 1-(4-chlorophenyl)-1-cyclopropyl-4-(4-fluoro-3-phenoxyphenyl butane, 6.

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

tribromide. In Figure 4, our alternative synthesis starts with elaboration of **8** by treatment with vinyl magnesium bromide to give 1-cyclopropyl-1-(4-chlorophenyl)-2-propen-1-ol, **10**, in 96% yield. Compound **10** is oxidized to 3-cyclopropyl-3-(4-chlorophenyl)propenal in 25% yield using either pyridinum chlorochromate or dichromate. This material is added to the Wittig reagent derived from (3-phenoxybenzyl)triphenylphosphonium chloride to give 1,3-butadiene, **11**, in 32% yield. Compound **11** is reduced to **6** in 92% yield using Raney nickel.

While this results in a more efficient and less time consuming synthesis, the low yields require still further improvement. Figure 5 details several improvements. This synthesis starts with **10**, which is treated with thionyl chloride to give 1-cyclopropyl-1-(4-chlorophenyl)-3-chloro-1-propene in 90% yield. Treatment with triphenyl phosphine gave the phosphonium salt, **12**, in 87% yield. Compound **12**, as a solid salt, is washed with toluene to remove many impurities, thereby allowing an easier purification of **11** when the Wittig reaction is performed (90% yield). The hydrogenation to **6** proceeds as described above.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

Biological Testing

The compounds were screened for insecticidal and acaricidal activity against the following species: cabbage looper (*Trichoplusia ni*), tobacco budworm (*Heliothis virescens*), Mexican bean beetle (*Epilachna varivestis*), pea aphid (*Acyrthosiphon pisum*), potato leafhopper (*Empoasca fabae*), brown planthopper (*Nilaparvata lugeus*), twospotted spider mite (*Tetranychus urticae*).

The activity against cabbage looper (CL), tobacco budworm (TBW) and Mexican bean beetle (MBB) was determined by spraying the upper and lower surfaces of the leaves of pinto bean plants with test solution until run-off and infesting with second instar larvae (ten larvae for each of two replicates for each compound) after the foliage had dried.

The activity against pea aphid (PA) was determined in a similar fashion, except that fava bean plants were used and the leaves were infested with adult aphids.

The activity against potato leafhopper (PLH) was determined in a similar fashion except that the treated fava bean plants were removed from their pots by cutting the stem just above the soil line. The excised leaves and stems were placed in petri plates and infested with two- to three-day-old potato leafhopper adults.

The activity against mites (TSM) was determined on pinto bean plants. The bean leaves were pre-infested with adult mites (about 75 mites for each of two replicates for each compound), then sprayed until run-off with test solution.

To prevent escape of the insects from the test site, the treated plant or excised leaves were placed in capped cups or other appropriate containers. The tests were transferred to a holding room at 25°C and 50% relative humidity for an exposure period of 48 hours. At the end of this time, percent mortality was determined and LC_{50} values were determined by probit analysis.

The activity against brown planthopper (BPH) was determined using TN1 rice plants that were 35-50 days old. The plants were trimmed to 1.0 feet and to contain four tillers. The plants were sprayed to run-off and allowed to dry. Twenty brown planthopper nymphs (2nd-3rd instar) were introduced per pot and covered with a mylar cage. Mortality readings were taken 24 hours after infestation, the LC_{50} values were determined by probit analysis.

Efficacy in residual testing was determined by spraying the test plants to run-off with aqueous dilutions of the compounds. The treated plants were held under greenhouse conditions for the appropriate period of time before infestation with insects. The test was then completed as described for the initial evaluations.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

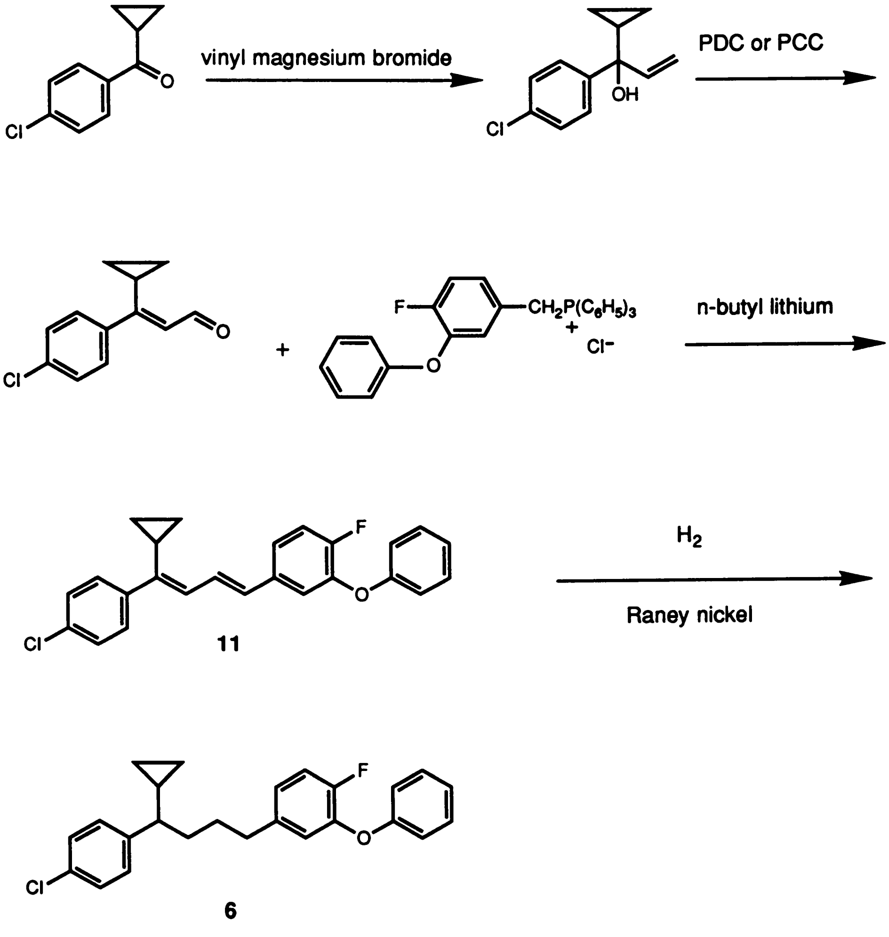

Cl
O
vinyl magnesium bromide
Cl
OH
PDC or PCC
Cl
O
+
F
CH₂P(C₆H₅)₃
+
Cl⁻
O
n-butyl lithium
F
Cl
O
11
H₂
Raney nickel
F
Cl
O
6

Figure 4. Improved synthesis of 1-(4-chlorophenyl)-1-cyclopropyl-4-(4-fluoro-3-phenoxyphenyl)butane, **6**.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

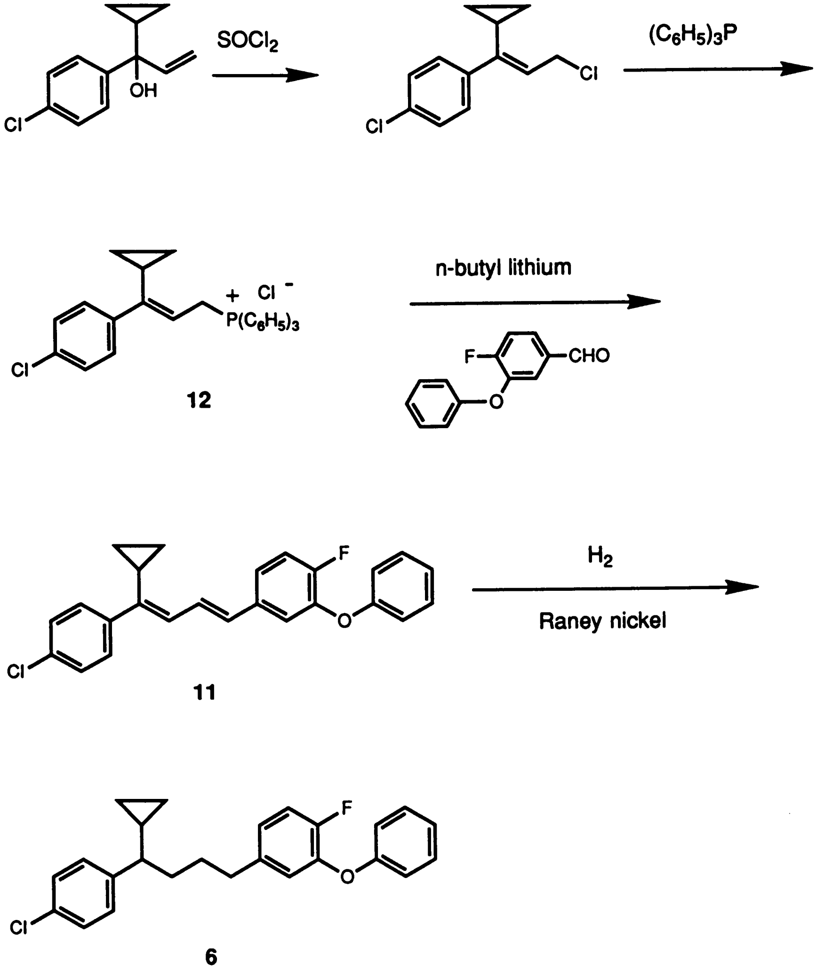

Cl
OH
$SOCl_2$
Cl
Cl
$(C_6H_5)_3P$
Cl
$+ Cl^-$
$P(C_6H_5)_3$
12
n-butyl lithium
F
CHO
O
Cl
F
O
11
H_2
Raney nickel
Cl
F
O
6

Figure 5. Final synthesis route to 1-(4-Chlorophenyl)-1-cyclopropyl-4-(4-fluoro-3-phenoxyphenyl)butane, 6.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

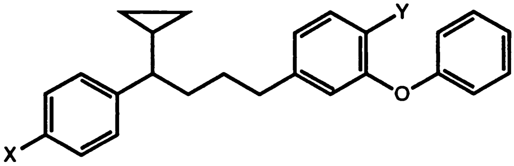
The fish toxicity was determined by testing against fathead minnows (*Pimephales promelas*) and common carp (*Cyprinus carpio*). Minnow testing required the test materials to be prepared as acetone (1%)/water solutions diluted to the appropriate volume, and allowed to equilibrate for five to six hours in one quart Mason jars before being infested with three fathead minnows (25-35 mm). Mortality counts were taken 24 hours after infestation.

The toxicity to carp was determined by Analytical Bio-Chemistry Laboratories Inc., Columbia, Missouri. The acute toxicity was assessed using the methods outlined by the Committee on Methods for Toxicity Tests with Aquatic Organisms. The test was conducted with duplicate 40 liter aquaria containing 30 liters of water with five fish per replicate chamber. A total of ten fish with a mean weight of 1.7 grams and a mean standard length of 39 millimeters were exposed to each test concentration and control. The 96 hour LC_{50} values were determined.

Results and Discussion

The efficacy of the 1-cyclopropyl-1-(4-substituted phenyl)-4-(3-phenoxyphenyl) butanes and 1-cyclopropyl-1-(4-substituted phenyl)-4-(4-fluoro-3-phenoxyphenyl) butanes as foliar insecticides is shown in Table I. This data shows that when Y is fluorine, the compound is consistently more active than when Y is hydrogen. However, such differences are not dramatic. Compound **3**, (X=Cl; Y=H or F)),

Table I. Foliar Activity of 1-Cyclopropyl-1-(4-X-phenyl-4-(4-Y-3-phenoxyphenyl) butanes



X	Y	LC_{50} (ppm)						
		Cabbage Looper	Tobacco Budworm	Pea Aphid	Mexican Bean Beetle	Two-spotted Spider Mte	Potato Leaf-hopper	Brown Plant Hopper
Cl	H	3	15	450	17	344	14	12
Cl	F	1	8	36	6	225	4	9
OCF_3	H	19	-	301	5	53	2	-
OCF_3	F	5	14	24	2	13	4	3
CF_3	H	13	33	17	23	123	9	5
CF_3	F	10	9	3	8	16	4	-
OC_2H_5	H	97	190	830	12	500	-	-
OC_2H_5	F	51	86	173	2	390	-	-
ethofenprox		97	7	51	14	310	6	31
MTI-800		16	15	33	2	-		

I = Inactive

provides a good illustration of this conclusion. In testing versus tobacco budworm, cabbage looper, and Mexican bean beetle, the fluoro analog is more active than the hydrogen analog but not to any great extent. Pea aphid and potato leaf hopper are more susceptible to the fluoro analog, but control of brown plant hopper is equivalent. Neither analog is effective against mites.

Compounds **3**, where X is equal to chloro, trifluoromethyl or trifluoromethoxy and Y is equal to fluorine, are judged by us to be the best overall insecticidal compounds in these tests. They are more active against cabbage looper than ethofenprox, and when X is chloro, more active than MTI-800. The tobacco budworm activity of these three compounds is equivalent to ethofenprox and MTI-800. In examining potato leaf hopper biological activity, these three compounds are equivalent to ethofenprox. Ethofenprox is less active against brown plant hopper (foliar LC_{50}=31 ppm) when compared to compounds **3**, where X is chloro and trifluoromethyl. The latter two compounds are active against brown plant hopper at LC_{50} rates of 9 ppm and 5 ppm, respectively. None of these compounds is particularly effective against mites. Further differentiation of these three compounds was not based on insecticidal activity, but upon other criteria, such as, aquatic testing data (*vide infra*).

In addition to good initial activity, it is necessary for a foliar insecticide to possess residual activity. Compound **6** has at least seven days residual activity against lepidoptera and that result is shown in Table II.

Table II. Residual Activity of **6**

Species	LC_{50} (PPM) 1 Day	 3 Days	 7 Days
CL	1	1	5
TBW	2	9	17

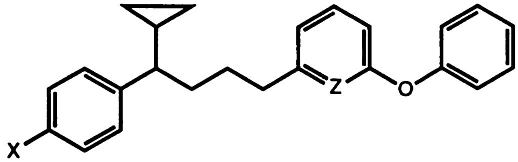
In Figure 2, it is shown that **Z** could either be nitrogen or carbon. An examination of the data in Table III shows that nitrogen does not contribute significantly to activity in the case of cabbage looper, pea aphid, Mexican bean beetle or potato leaf hopper. From this biological data we conclude that the pyridyl analogs do not offer any advantage relative to the corresponding phenyl analogs.

In our earlier work on cyclopropyl aryl oxime ethers, we showed **13**, which contained the 2-methyl-1,1'-biphenyl fragment, was more active than **5**, which contained 3-phenoxyphenyl fragment (*5*). In this project we wished to determine whether the 2-methyl-1,1'-biphenyl fragment contributed to activity to a greater extent than the corresponding 3-phenoxyphenyl and the 4-fluoro-3-phenoxyphenyl fragments. The insecticidal data for these 2-methyl-1,1'-biphenyl compounds, **14**, is in Table IV. When these compounds are compared with the corresponding 3-phenoxyphenyl and the 4-fluoro-3-phenoxyphenyl analogs shown in Table I, it is evident that the 3-phenoxyphenyl and the 4-fluoro-3-phenoxyphenyl fragments are more active as foliar insecticides than the compounds containing the 2-methyl-1,1'-biphenyl fragment. Table V illustrates that conclusion with a series of analogs where X is chloro. In general, the compounds **6** and **3** (X=Cl, Y=H or F) are more active than **14**, except in foliar testing against pea aphids, where **3** (X=Cl, Y=H) is less active than **14**.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

Table III. Pyridyl Analog Insecticidal Activity (LC_{50} ppm)



X	Z	Cabbage Looper	Pea Aphid	Mexican Bean Beetle	Potato Leaf-hopper
Cl	C	3	450	17	14
Cl	N	3	26	11	11
CF_3	C	13	17	23	9
CF_3	N	14	28	4	6
ethofenprox		97	51	14	6
MTI-800		16	33	2	-

Table IV. Insecticidal Activity of Derivatives of 14 (LC_{50} ppm)

X	Cabbage Looper	Tobacco Budworm	Mexican Bean Beetle	Pea Aphid
Cl	15	114	185	92
CF_3	42	287	72	22
OC_2H_5	270	150	81	475

Table V. Comparison of Foliar Activity of Analogs of 3 and 14 (LC_{50} ppm)

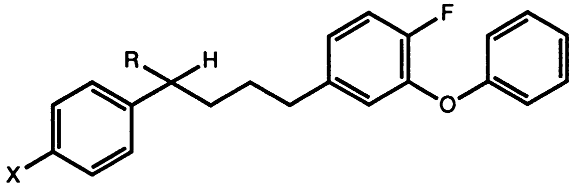
Compound	X	Y	Cabbage Looper	Tobacco Budworm	Mexican Bean Beetle	Pea Aphid
3	Cl	H	3	15	17	450
6	Cl	F	1	8	6	36
14	Cl	-	15	114	185	95

Table VI shows that the cyclopropyl group is essential for topical and foliar activity on our compounds. In topical testing, the cyclopropyl analog where X is chloro has a topical LD_{50} of 55 µg g^{-1} whereas the isopropyl analog has no control at 1000 µg g-1. The foliar activity shows the same relationship, as the cyclopropyl analog has a foliar LC_{50} of 1 ppm and the isopropyl analog has a foliar LC_{50} of 180 ppm. In this area as in the cyclopropyl aryl oxime ethers, it has been shown that the cyclopropyl group is essential for good topical and foliar activity. Surprisingly, the cyclopropyl compounds where X is equal to chloro and ethoxy are equivalent in topical activity (Table VI), but are different in foliar activity (Table I and Table VI). The foliar LC_{50} is 1 ppm for the chloro analog and 51 ppm for the ethoxy analog against cabbage looper. In this test, MTI-800 had the best topical activity

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

(LD_{50}=19 μg g^{-1}), yet the foliar LC_{50} was 16 ppm. This suggested that good topical activity contributes to foliar control of cabbage looper, but it is not the only factor involved.

Table VI. Comparison of Cyclopropyl Versus Isopropyl



		Cabbage Looper	
		Topical	Foliar
R	X	LD_{50} (μg g^{-1})	LC_{50} (ppm)
Cyclopropyl	Cl	55	1
Isopropyl	Cl	0% @ 1000 μg g^{-1}	180
Cyclopropyl	OC_2H_5	50	51
MTI-800		19	16

Fish Toxicity

To assess safety to fish, we determined the static toxicity of two compounds to fathead minnows. On the basis of their broad spectrum foliar activity, two compounds were selected: **6** and **3**, where X=CF_3. The results are reported in Table VII. Compound **3**, where X=CF_3, is relatively less safe than **1** and was dropped from further consideration. Further testing of compound **6** against carp shows it to have fish safety equivalent to ethofenprox and MTI-800 in this test as seen in Table VIII.

Table VII. Aquatic Testing with Fathead Minnow

Compound	Static LC_{50} (ppb)
3 (X=CF_3)	9
6	> 50
ethofenprox	38
cypermethrin	1

Table VIII. Aquatic Testing with Carp

Compound	Static LC_{50} (ppb)
ethofenprox	5*
MTI-800	>40*
6	>30

*Reference (1)

Mammalian Toxicity

With good insecticidal activity and relative safety to fish, an additional parameter to evaluate was acute toxicity. Our criteria for acceptable toxicity were acute oral and dermal toxicity comparable to or better than ethofenprox and MTI-800. The results in Table IX show the relative safety to mice by **6** desired at the outset of the project.

Table IX. Results of Mammalian Toxicity Testing

Compounds	Acute Oral LD_{50} (mg/kg)	Acute Dermal LD_{50} (mg/kg)
1	>300*	>2100**
2	>300*	–
6	50-500	200-2000

*Reference 1

Conclusions

The 1-cyclopropyl-1-(4-substituted phenyl)-4-(4-fluoro-3-phenoxyphenyl)butanes are effective foliar insecticides with good initial and residual activity against worms. These compounds are also effective against hoppers and can be considered potential rice insecticides. Finally, these compounds as illustrated by **6** are equivalent to ethofenprox and MTI-800 in their relative safety to fish and mammals.

Acknowledgments

The authors acknowledge the contributions of our many co-workers in this program. Charles M. Langevine prepared several compounds; Kathleen A. Boyler, Michael A. Walsh, Mina Reed, Carmela E. Williams, George L. Meindl, and Lisa A. Schultz were responsible for the insecticide data; Annette C. Slaney helped perform the fathead minnow evaluation; Susan A. Meissner aided in manuscript preparation. Finally, the authors acknowledge the support of FMC Corporation.

Literature Cited

1. Meier, G. A.; Sieburth, S. M.; Cullen, T. G.; Engel, J. F. (FMC Corporation) U.S. Patent 4,808,762, 1989.
2. Sieburth, S. M.; Lin, S. Y.; Cullen, T. G. *Pestic. Sci.* **1990**, *29*, 215.
3. Holan, G.; Johnson, W. M. P.; O'Keefe, D. F.; Quin, G. L.; Rihs, K; Spurling, T. H.; Wolser, R.; Virgona, C. T.; Frelin, C.; Lazdunski, M.; Johnston, G. A. R.; ChenChow, S.; *In Recent Advances in the Chemistry of Insect Control*, Edited by James, N. F.; The Royal Society of Chemistry: London, 1985.
4. Cullen, T. G.; Manly, C. J.; Cruickshank, P. A.; Kellar, S. M.; *In Synthesis and Chemistry of Agrochemicals*; Edited by Baker, D. R.; Fenyes, J. G.; Moberg, W. K.; Cross, B.; American Chemical Society: Washington, D.C., 1987
5. Elliot, M.; Farnham, A. W.; James, N. F.; Johnson, D. M.; Pilman, D. A.; *Pestic. Sci.* **1980**, *11*, 513.
6. Udagawa, T.; Nakatani, K.; Inoue, T.; Numata, S.; Oda, K.; Gohbana, M.; *The Fifth International Conference of Pesticide Chemistry*: Kyoto Japan, **1982.**
7. Udagawa, T.; Numata, S.; Oda, K.; Shiraishi, S.; Kodaka, K.; Nakatani, K.; *In Recent Advances in the Chemistry of Insect Control*, Edited by James, N.F.; The Royal Society of Chemistry: London, 1985.

RECEIVED July 6, 1992

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch024

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

Chapter 25

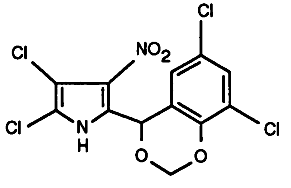
Insecticidal Pyrroles

Discovery and Overview

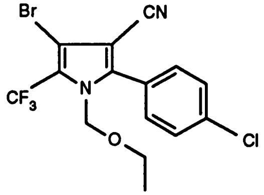
R. W. Addor, T. J. Babcock, B. C. Black, D. G. Brown, R. E. Diehl, J. A. Furch, V. Kameswaran, V. M. Kamhi, K. A. Kremer, D. G. Kuhn, J. B. Lovell, G. T. Lowen, T. P. Miller, R. M. Peevey, J. K. Siddens, M. F. Treacy, S. H. Trotto, and D. P. Wright, Jr.

Agricultural Research Division, American Cyanamid Company, P.O. Box 400, Princeton, NJ 08543–0400

Dioxapyrrolomycin, isolated from a *Streptomyces* strain, was found to have moderate activity against a number of insects and mites and to be a potent uncoupler of oxidative phosphorylation. These findings, along with the novel structure, led to a search for acidic halogenated nitropyrroles, and pyrroles with other substituent combinations, with useful insecticidal or other pesticidal activity. A progession of new pyrroles described here has led to AC 303,630 which has been chosen for commercial development as a broad-spectrum insecticide/miticide.



Dioxapyrrolomycin



AC 303,630

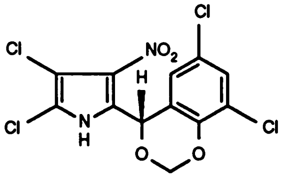
Chemists and biologists who have been involved with the search for new ways to control insects have also been challenged with making that effort as specific as possible for the pest to be controlled. Thus much attention has been paid to modes of action which are specific for invertebrates and would, presumably, spare mammals. On the other hand, finding any new strategy whether chemical or biological which succeeds in holding off the onslaught of the major insect pests remains a daunting challenge.

Put another way, strictly from the chemists point of view, finding new chemistry that works and offers some advantage over existing control agents is a difficult proposition. Described in part here is a particular effort to find an effective and acceptable new insecticide whose mode of action is at the cellular level, that is, one whose principle action is as an uncoupler of oxidative phosphorylation.

0097–6156/92/0504–0283$06.00/0

Pyrrolomycins

Of course, we did not choose the mode of action and proceed from there to design a new insecticide. The impetus came from our ongoing insecticide screening program. The lead in this case was an unusual one, having been discovered through the efforts of Cyanamid's fermentation program conducted at the Lederle Laboratories in Pearl River, New York. By screening broths against insects and by the usual methods of coupling biological activity with isolation techniques, the Lederle scientists isolated from a *Steptomyces* strain and identified the compound shown in Figure 1 (*1*). At about the same time, this pyrrole was also reported by Meiji Seika Kaisha and the SS Pharmaceutical Company in Japan (*2, 3*) as an antibiotic. Neither made mention of insecticidal activity. It has been named dioxapyrrolomycin. As shown in Figure 1, dioxapyrrolomycin exhibited moderate broad spectrum insecticidal and miticidal activity. However, an oral LD_{50} of 14 mg/kg to mice showed it to be highly toxic. This combination did not make dioxapyrrolomycin a candidate for development, but the structure was simple enough to warrant consideration as a take-off for synthetic modification.



Pesticidal Activity

Species	LC_{50} ppm*
Southern Armyworm (*Spodoptera eridania*):	40
Tobacco Budworm (*Heliothis virescens*):	32
2-Spotted Mite (*Tetranychus urticae*):	10
Western Potato Leafhopper (*Empoasca abrupta*):	>100

*Leaf-dip assay

Figure 1: Dioxapyrrolomycin

Dioxapyrrolomycin is a recent addition to a series of antibiotic pyrroles largely isolated and identified by Meiji Seika Kaisha scientists and generically called pyrrolomycins. Several are shown in Figure 2 (*4, 5*). Except for pyrrolomycin D, which has three pyrrole ring halogen atoms, they share a nitro substituent along with halogen atoms. Again, varying degrees of antibacterial and antifungal activities are attributed to these compounds and several others of similar structure, but there has been no indication of insecticidal or miticidal activity.

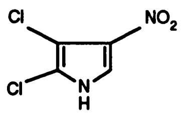
Oxidative Phosphorylation Uncouplers

We suspected that the pyrrolomycins would be good uncouplers of oxidative phosphorylation. When put to the test, using rat liver mitochondria as the substrate and measuring oxygen uptake, dioxapyrrolomycin was, in fact, shown

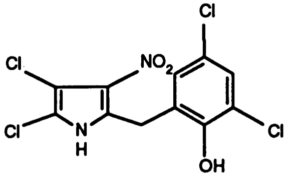
Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

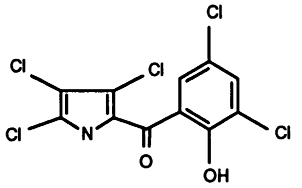
to be a potent uncoupler with an I_{50} of .025 μmolar. Several pesticides known to function as uncouplers are shown in Figure 3. Of these compounds, dinocap is representative of a number of dinitrophenols and their derivatives which have found utility as acaracides and herbicides. The salicylanilide, niclosamide, is effective in controlling snails (*6*). The benzimidazole, fenazaflor, appears to have been given serious consideration for development by Shell scientists some years ago as an acaricide (*7*). More recent is work reported by Morton of ICI (*8*) on the diarylamine acaricide fentrifanil shown later by Nizamani and Hollingworth to be a potent uncoupler (*9*). Work with a similar series of compounds has been described more recently by Eli Lilly scientists as well as by other groups (*10, 11*).



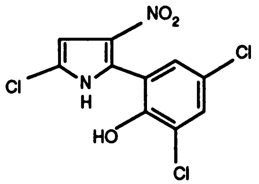
Pyrrolomycin A



Pyrrolomycin B

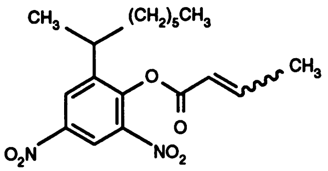


Pyrrolomycin D

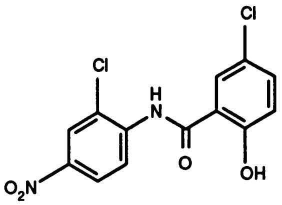


Pyrrolomycin E

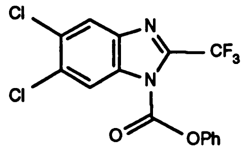
Figure 2: Pyrrolomycins



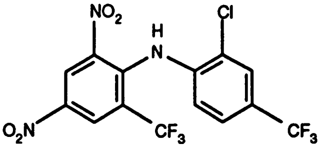
Dinocap



Niclosamide



Fenazaflor



Fentrifanil

Figure 3: Respiratory Inhibitors

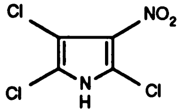
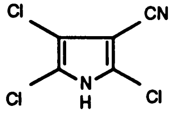
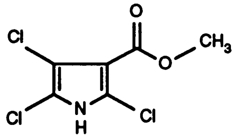
Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

Effective uncouplers share two important properties. The first is that they are weak acids. Peter Heytler suggests a pka in the general region of 4.5 to 6.5 (*12*). At the same time they are highly lipophilic. These properties appear to allow such compounds to short-circuit the proton gradient across membranes within mitochondria. The net result is that oxidative processes normally designed to convert ADP to ATP, the energy source within cells, becomes disengaged and the cell dies. Of the compounds in Figure 3 dinocap and fenazaflor must be considered as pro-pesticides, hydrolysis being required to produce the acidic phenol or benzimidazole which acts as the uncoupler. In both cases, derivatization serves to reduce the phytotoxicity of the parent compound. An uncoupler may be as damaging to the functioning of a plant's chloroplasts as it is to an animals mitochondria (*13*).

Synthesis and Pesticidal Evaluation

As a base line, and to tell us if a nitro group was of special significance, the three trichloropyrroles shown in Table I were synthesized. The simple nitro and cyanopyrroles showed activity, with the cyanopyrrole the better of the two. The ester showed no activity. 3-Nitrotrichloropyrrole had been reported by Meiji Seika (*4*). Surprisingly, neither trichloro nor tribromo 3-cyanopyrroles had been reported in the literature.

Table I: Trichloropyrroles

	Army-worm[a]	Bud-worm[a]	Mite[b]	Leaf-hopper[c]
	+	0	+ ±	0
	+ + ±	+	+ ±	+
	0		0	

(a) Complete kill at: 1000 ppm (+), 100 ppm (++), 10 ppm (+++), 1 ppm (++++) by leaf-dip assay.

(b) Complete kill at: 100 ppm (+), 10 ppm (++), 1 ppm (+++) by leaf-dip assay.

(c) Complete kill at: 300 ppm (+), 100 ppm (++), 10 ppm (+++) by leaf-dip assay.

In work directed more toward the dioxapyrrolomycin structure itself, 2-benzyl-3-cyanopyrrole was prepared as shown in Figure 4 (*14*). In the course of chlorination, the benzyl methylene group was oxidized and the benzoyl derivative shown, isolated in low yield, demonstrated some insecticidal activity. Based on this result and consideration of the structure of pyrrolomycin D, 2- and 3-para-chlorobenzoylpyrroles were prepared by literature methods (*15*, *16*). Halogenation gave the additional structures shown in Figure 4. As indicated, neither compound proved especially active. As a further structural simplification,

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

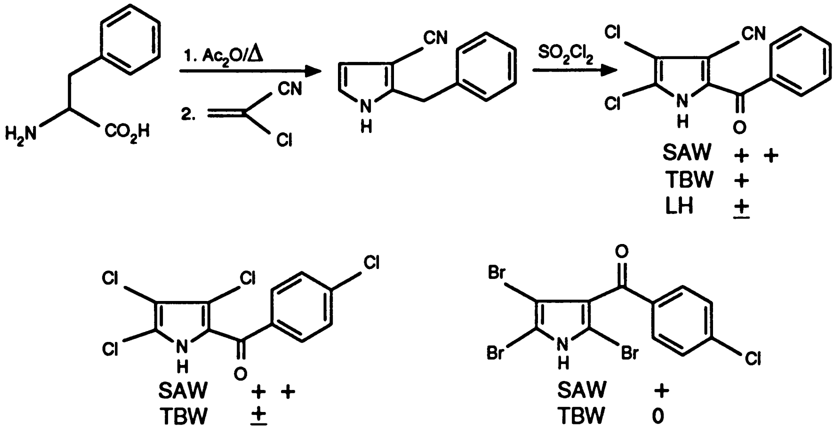


Figure 4: Benzoylpyrroles

2-phenyl-3-cyanopyrrole was prepared utilizing phenylglycine in place of benzylglycine in the scheme in Figure 4 (*14*). Chlorination provided 2-phenyl-3-cyano-4,5-dichloropyrrole (**1**, Table II). As shown in Table II, **1** was found active against lepidopterous larvae providing impetus for additional work. However, to facilitate preparation of a large number of both cyano- and nitro-containing analogs of **1**, a new synthesis strategy was needed. This requirement was met by development of the route shown in Figure 5, one which succeeded in providing good yields for both series of compounds. This scheme has a close analogy in work reported to afford 2-benzoyl- and 2-alkylthio-3-nitropyrroles (*17*).

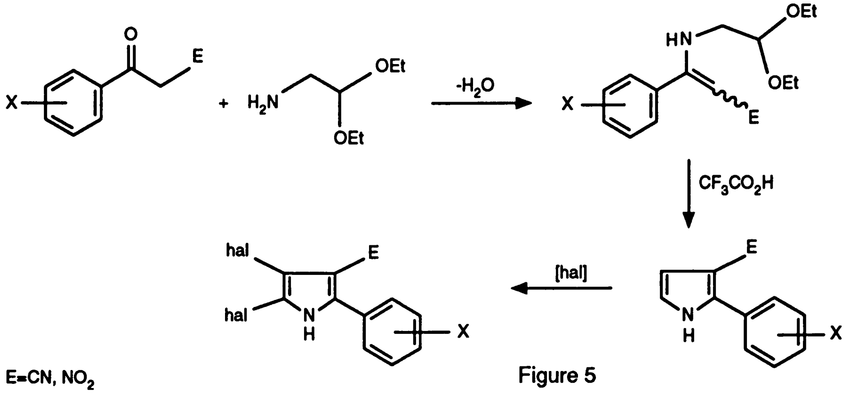


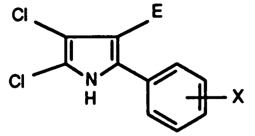
Figure 5

By this new process, a range of 2-aryl-3-cyano and 3-nitro dichloro and dibromo pyrroles as represented in Table II was prepared for testing. The 4,5-dichloro compounds are shown; there was little difference in activity noted between these and their 4,5-dibromo counterparts. Compounds incorporating halogen atoms on the phenyl ring were found to have good activity against the army worm and the tobacco budworm. With compounds such as **3**, **4** and **5** we had achieved activity against lepidopterous larvae superior to that of dioxapyrrolomycin and, at the same time, improved on the mouse toxicity. But

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

leafhoppers and mites were unaffected at test levels except for the nitropyrrole **6**. Notably, the *p*-tolyl compound **7** was inactive possibly due to metabolic loss. At least part of the answer may also lie in the reduced acidity of the pyrrole. The numbers at the bottom of Table II show that the pyrrole pka is significantly affected by the phenyl ring substituent with over a pka unit difference between the *p*-chloro phenyl and the *p*-tolyl analogs.

Table II: 2-Aryl-3-Cyano/Nitro Pyrroles



	X	E	Army-[a] worm	Bud-[a] worm	[a] Mite	Leaf-hopper
1.	H	CN	+ +	+	0	0
2.	H	NO_2	+ +	+ ±	0	0
3.	4-Cl	*CN	+ + + (5.4)[a]	+ + (24)	0	0
4.	4-Cl	NO_2	+ + + (8.0)	+ + (21)	+	0
5.	3,4-di-Cl	**CN	+ + + (4.7)	+ + (15)	0	0
6.	3,4-di-Cl	NO_2	+ + + (8.2)	+ + (63)	0	+ +
7.	4-CH_3	***CN	0	0	0	0
8.	4-CF_3	CN	+ + + (1.0)	+ + + (9.4)	+ + + (7.0)	+
9.	4-CF_3	NO_2	+ + + (10.7)	+ + (41)	+ + + (19)	+
10.	4-OCF_3	CN	+ + + (4.5)	+ + (23)	+ + (9.1)	+ +
11.	4-CO_2CH_3	CN	+	±	0	0
12.	4-NO_2	CN	+ +	+ ±	0	0
Dioxapyrrolomycin			+ + (40)	+ + (32)	+ + ± (10)	+ ±

*pka=6.3; clog P=4.8 **pka=6.1; clog P=5.7 ***pka=7.4; clog P=4.7

(a) Numbers in parentheses are LC_{50} values in ppm.

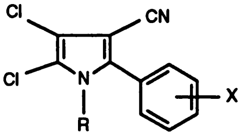
Of the compounds in Table II, the 2-(3,4-dichlorophenyl)-3-cyanopyrrole **5** was selected for limited field evaluation. On cotton, **5** showed interesting but uneconomic control of the *Heliothis* species. However, for lepidopterous larvae on cabbage it was effective at 0.25 kg/ha. Also, in field applications, **5** proved outstanding for the control of resistant Colorado potato beetle at 125 g/ha. These results indicated that certain pyrroles, even though based on a heterocycle not especially noted for its oxidative or photolytic stability, could be made to work effectively as insecticides in the field.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

The introduction of a trifluoromethyl or a trifluoromethoxy group on the aromatic ring in this series to give compounds **8**, **9**, and **10** had the rather dramatic effect of regaining the miticidal activity shown by dioxapyrrolomycin but missing for most of the members of the 2-aryl-3-cyano series. However, there was a drawback since, unlike **5**, these compounds were highly phytotoxic. Consequently we were drawn to the need to examine N-derivatization of these pyrroles. As with the earlier described phenol and benzimidazole examples, pesticidally effective derivatives would be metabolized to the parent pyrrole within the insect. Uncoupling activity, which we expected for the active compounds in Table II, was verified by oxygen electrode experiments. For instance, with rat liver mitochondria, pyrrole **5** was shown to have a pI_{50} of 2 nanomolar. Consistent with this mode of action, experiments with a spruce budworm cell line showed **5** and close analogs to be cytotoxins at the sub-micromolar level.

Some results of N-derivatization on insecticidal activities are shown in Table III. Clearly, with the dichlorophenylpyrrole series, the worm activity noted for the parent compound **5** is retained by a variety of derivatization products. A surprise resulted when an alpha-methyl group was introduced into the alkoxymethyl substituent, *e.g.*, to give compound **20**. In this case worm activity was retained but, unlike **5** itself and the other derivatives, good activity was also found for both the mite and leaf hopper. Introducing the ethoxymethyl group into

Table III: N-Derivatization



R	Army-worm[a]	Bud-worm[a]	Mite[a]	Leaf-hopper[a]
X=3,4-di-Cl				
5. H	+ + +	+ + (15)	0	0
13. CH_3	+ + +	+ +	0	0
14. CH_2Ph	+ + +	+	0	0
15. CN	+ + +	+	0	0
16. CH_2CN	+ + +	+ + +	0	0
17. CH_2CO_2Et	+ +	+	0	0
18. $CONMe_2$	+ + +	+ +	0	0
19. $CH_2OC_2H_5$	+ + +	+ +	0	0
20. $CHOCH_3$ | CH_3	+ + + (3.6)	+ + ± (14)	+ +	+ + (3.5)
X=4-CF_3				
7. H	+ + + (1.0)	+ + + (9.4)	+ + + (7.0)	+
21. $CH_2OC_2H_5$	+ + + (2.7)	+ + + (10)	0	+ + + (2.0)

(a) Numbers in parentheses are LC_{50} values in ppm.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

the *p*-(trifluoromethyl)-phenylpyrrole **7** to give compound **21** also produced an interesting result, *i.e.*, the high activity noted for **7** against the mite was lost while leaf hopper activity was markedly improved. In the effort to eliminate phytotoxicity through such N-derivatization, the grasses, including rice, gained tolerance with **21** but the broadleaves retained their susceptibility. We were also pleased to note that compound **21**, among the most potent and broadly active pyrroles prepared up to that time, was also one of the safest, with a mouse oral LD_{50} of 144 mg/kg. This was evidence that mammalian toxicity for these new pyrroles need not go hand-in-hand with their insecticidal potency.

In addition to examining effects of phenyl ring substituents on insecticidal potency and range, we needed to look at the isomer picture on the pyrrole ring. Confining the search to an aromatic ring, a cyano or nitro group, and two halogens around the pyrrole ring affords six regioisomers for consideration. If a fourth substituent replaces a halogen atom, then one is forced to deal with twelve regioisomers.

To provide 2-aryl-4-cyanopyrroles, an adaptation of the recently described procedure of Tsuge and coworkers shown in Figure 6 was used (*18*). It is lengthy and limited in range by the availability of aryl Grignard reagents. Nevertheless, this procedure, followed by halogenation, provided the initial examples which afforded good worm activity. We searched for an improved synthesis and succeeded with the second scheme shown in Figure 6. Interestingly, *beta*-benzoylpropionitrile itself with hydrogen chloride in benzene, is reported to form only the imidoyl chloride (*19*). Also, using concentrated hydrochloric acid in acetic acid, Abdelhamid and coworkers have recently reported that phenacylmalononitrile gives only 2-amino-3-cyano-5-phenylfuran (*20*). This is a minor by-product under the conditions we used.

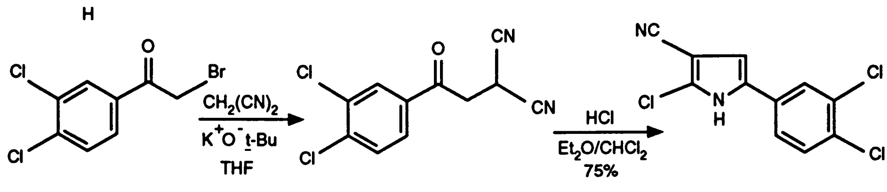


Figure 6: 2-Aryl-4-Cyanopyrroles

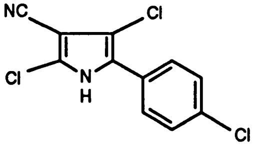
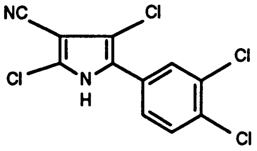
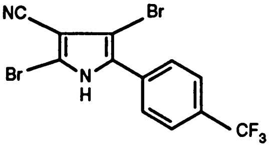
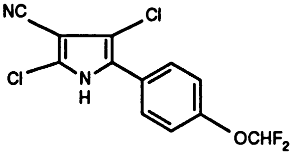
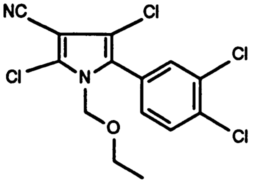
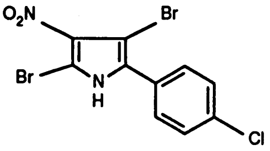
Activities for some representative 2-aryl-4-cyano compounds are shown in Table IV. Again, electron withdrawing groups on the aromatic ring promote insecticidal activity. In most instances, the underivatized pyrroles in this group had activity largely limited to lepidopterous larvae. Whereas the *para*-(trifluoromethyl)phenyl analog in the 2-aryl-3-cyano series had shown excellent two-spotted mite activity, the 2-aryl-4-cyano counterpart **24** was

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

inactive on this pest. As before, the experience of N-derivatization offered interesting and useful results. Thus compound **26**, the N-ethoxymethyl derivative of **23**, is highly active against all the species shown. Although slightly more phytotoxic than some of our other candidates, it has undergone considerable evaluation and remains one of our more effective insecticidal pyrroles.

Of additional interest was the finding that comparable 2-aryl-4-nitro analogs, as represented here by compound **27**, are significantly less active than their cyano counterparts, in this case compound **22**.

Table IV: 2-Aryl-4-Cyanopyrroles

		Army-worm [a]	Bud-worm [a]	Mite [a]	Leaf-hopper [a]
22.		+ + +	+ +	0	±
23.		+ + +	+ +	±	0
24.		+ + +	+ +	0	0
25.		+ + ±	+ +	0	±
26.		+ + + (3.6)	+ + ± (7.3)	+ + + (6.0)	+ + (2.2)
27.		+	+	±	0

(a) Numbers in paretheses are LC$_{50}$ values in ppm.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

The additional four regioisomeric aryl/cyano pyrroles were prepared by the schemes shown in Figure 7. Chlorination of the appropriate pyrroles obtained by these procedures and those described earlier afforded the examples represented in Table V.

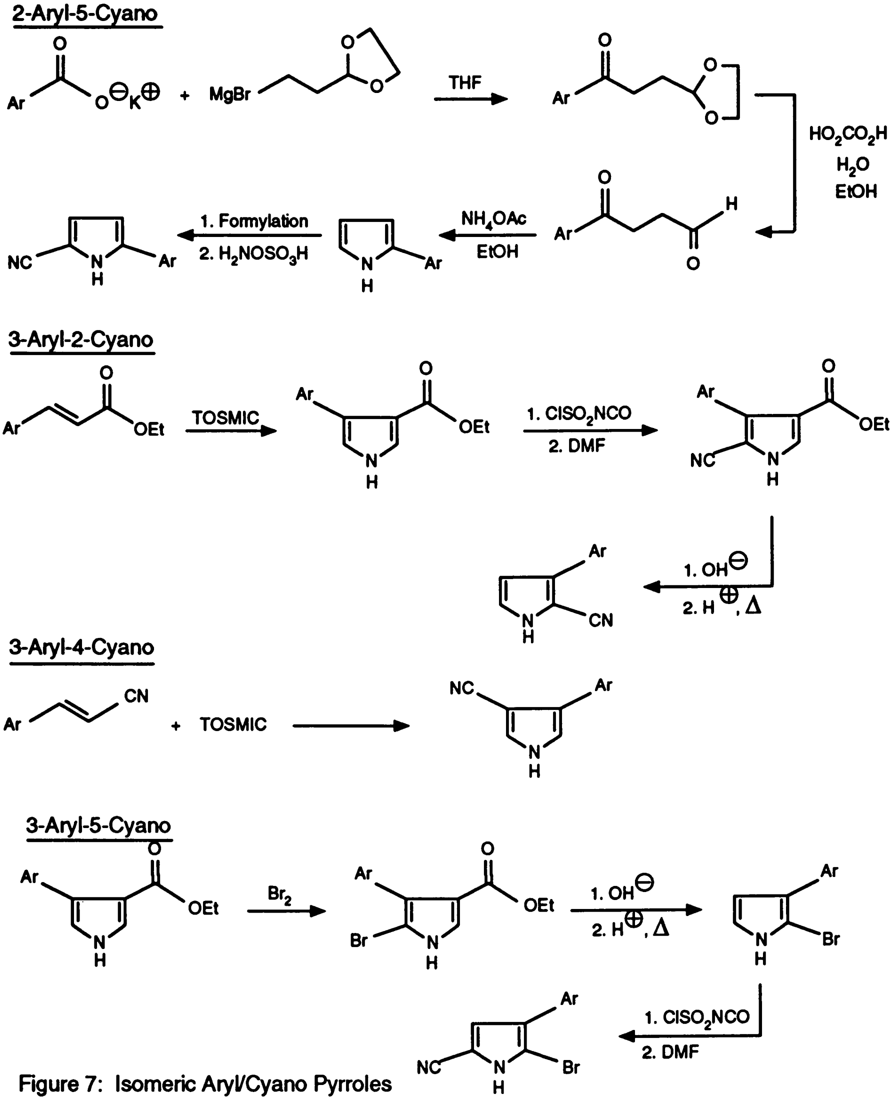
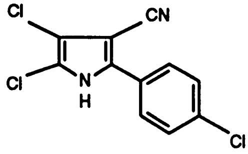

2-Aryl-5-Cyano
Ar
O⊖K⊕
+ MgBr
THF
HO₂CO₂H
H₂O
EtOH
NH₄OAc
EtOH
1. Formylation
2. H₂NOSO₃H
NC
N
H
3-Aryl-2-Cyano
OEt
TOSMIC
1. ClSO₂NCO
2. DMF
1. OH⊖
2. H⊕, Δ
CN
3-Aryl-4-Cyano
+ TOSMIC
3-Aryl-5-Cyano
Br₂
Br

Figure 7: Isomeric Aryl/Cyano Pyrroles

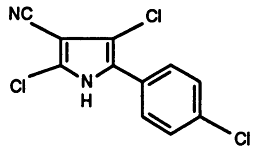
Like the 2-aryl-3-cyano and 2-aryl-4-cyanopyrroles, the 2-aryl-5-cyano compounds also showed good worm activity. However, when the aryl group was moved to the 3-position of the pyrrole ring, activity dropped off generally ten-fold or more. As pointed out earlier, the 2-aryl-4-nitro isomer was less active than the 2-aryl-3-nitro compound. With these aryl-nitro pyrroles, moving the aryl group to the 3-position was also detrimental to activity.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

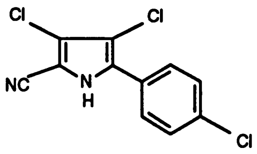
Table V: Isomeric Aryl/Cyano Pyrroles



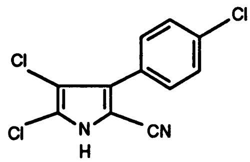
SAW + + +
TBW + +



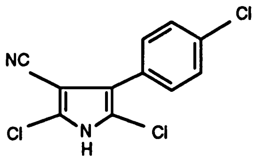
SAW + + +
TBW + +



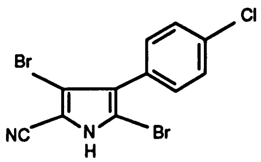
SAW + + +
TBW + +



SAW + +
TBW +



SAW +
TBW +

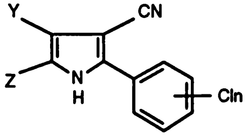


SAW + +
TBW +

Table VI shows, for the 2-aryl-3-cyanopyrrole type, the effect of some additional variation around the ring. Removal of either of the halogen atoms to give compounds **28** and **29** resulted in a ten-fold loss of activity against lepidopterous larvae. Of the three dinitriles shown, **30**, **31** and **32**, compound **31**, with a hydrogen in the 4-position was the most active against the army worms matching the lead compound **5**. In this case, the addition of the bromine atom to give **32** was not beneficial to worm activity but did generate some action against mites. Introduction of a nitro or acetyl group as shown with **33**, **34** and **35** was of little help. A methyl group in the five position destroyed activity. Compared to a halogen atom, such a change has the effect of increasing the pka of the pyrrole by about 4 units and is likely the major reason for loss of activity.

With many biologically active compounds the replacement of a halogen by a trifluoromethyl group often results in an enhanced biological response (*21*). A number of such replacements were achieved in the current work including putting the trifluoromethyl group in the five-position of a 2-aryl-3-cyanopyrrole to afford **37**. The results are as shown in Table VII. Compared to the earlier 4,5-dihalopyrroles, the new compound proved not only more toxic to the tobacco budworm, but, in addition, was highly active against the two-spotted spider mite and the potato leafhopper. The pka of **37** is 5.6; the calculated logP is 5.6. These numbers are not much different from those for the dichloro analog **5**, which has a pka of 6.1 and a calculated logP of 5.7.

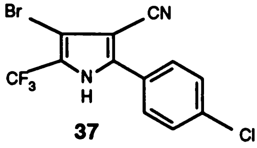
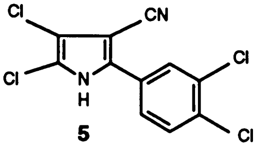
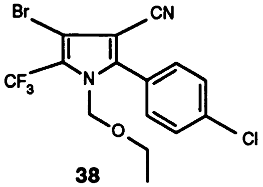
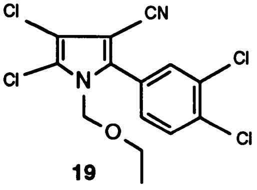
Table VI: Substituent Effects



n = 1,2

	Y	Z	Army-worm	Bud-worm	Mite	Leaf-hopper
5	Cl	Cl	+ + +	+ +	0	0
28	Cl	H	+ +	+	+	0
29	H	Br	+ +	+	0	0
30	CN	Cl	+ +	+	0	0
31	H	CN	+ + +	+ ±	0	0
32	Br	CN	+ +	+ ±	+ +	±
33	Br	NO_2	+ +	+	0	0
34	NO_2	Br	+ +	+	0	0
35	Br	$COCH_3$	+ +	0	0	0
36	Br	CH_3	0	0	0	0

Table VII: 2-Aryl-3-Cyano-5-CF_3 Pyrroles

	Army-worm[a]	Bud-worm[a]	Mite[a]	Leaf-hopper[a]
 **37**	+ + + (3.5)	+ + + (3.6)	+ + + (2.9)	+ + (4.9)
 **5**	+ + + (4.7)	+ + (15)	0	0
 **38**	+ + + (2.6)	+ + + (7.5)	+ + + + (1.6)	+ + ± (0.92)
 **19**	+ + + (2.5)	+ + (17)	0	0

(a) Numbers in parentheses are LC_{50} values in ppm.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

We once again found ourselves with a severe phytotoxicity problem. However, when the ethoxymethyl derivative **38** (Table VII) was prepared, the compound proved safe not only to grasses, but to broadleaves as well. In addition, there was no loss of activity against the pest species tested. The chemistry which provided **38**, which we have designated AC 303,630, as well as some additional work done around it is discussed in the accompanying paper by D. G. Kuhn and coworkers is discussed in the companion chapter of this volume by D. G. Kuhn and coworkers.

The oral LD_{50} of AC 303,630 to rats (combined sexes) is 662 mg/kg. Dermal toxicity to rabbits exceeds 2000 mg/kg. The LC_{50} for Japanese carp is 0.5 ppm. The compound is non-mutagenic in the modified Ames test and the Chinese hampster ovary test.

Table VIII shows a comparison of the activity of AC 303,630, cypermethrin, and other standards applied as a leaf dip to cotton and fed to third instar tobacco budworms (*22*). In this test AC 303,630 and cypermethrin are of equal activity and 4 to 16 fold more active than the other standards. Against first instar worms, AC 303,630 is about 1.4 times less active than cypermethrin, as active as methomyl and profenofos, and superior to the other three. By contact of residues on glass it is about 10 fold less active than cypermethrin, 2 to 3 below that of endosulfan and profenophos, and about equal to methomyl and sulprofos (*22*).

Table VIII: Toxicity of Selected Insecticides to Third Instar Tobacco Budworms in a Leaf-dip Assay

Treatment	n^1	LC_{50} in ppm (95% CI)	
AC 303,630	89	7.50	(6.69- 8.46)
Cypermethrin	148	7.54	(4.48-11.73)
Methomyl	148	31.77	(26.09-39.50)
Profenofos	143	32.46	(27.37-37.28)
Sulprofos	318	42.79	(19.39-99.85)
Acephate	147	45.31	(39.09-51.52)
Endosulfan	113	125.37	(96.28-208.81)

[1] Number of larvae tested, excluding controls. Source: Reprinted with permission from ref. 22. Copyright 1991.

A summary of some field results versus standards in cotton field trials in Brazil and the USA is shown in Table IX (*23*). Standards against *Tetranachychus urticae* and *Polyphaqotarsonemus latus* were Abamectin at 0.011 kg/ha and propargite at 1.08 kg/ha. Cypermethrin at 0.056-0.067 kg/ha, deltamethrin at 0.005 to 0.01 kg/ha, cyfluthrin at 0.028 kg/ha, and esfenvalerate at 0.034 kg/ha served as standards for the other species shown. A rate of 0.125 kg/ha of AC 303,630 was sufficient to control all but the *Heliothis/Helicoverpa spp.*, a rate of 0.250 kg/ha being required for this species.

Table IX: Summary of AC 303,630 vs. Standard Treatments - Comparative Results of 1988-89 Cotton Field Trials Conducted in Brazil and the USA

Pest (No. of trials)	AC 303,630 Rate (kg AI/ha) Providing Control >= Standard (P=.05)
Tetranychus urticae (5)	0.125
Polyphagotarsonemus latus (2)	0.125
Alabama argillacea (1)	0.125
Heliothis/Helicoverpa spp. (9)	0.250

Source: Reprinted with permission from ref. 23. Copyright 1990.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

In the laboratory, AC 303,630 has been shown to retain its activity against two different strains of pyrethroid-resistant tobacco budworms at both the first and third instar stages (*22*). Limited fieldwork with a resistant strain confirms this result.

The range of activity of AC 303,630 is further shown in Table X for work conducted on vegetables and sugar beets in Brazil, Canada, Italy, the U.K. and the USA (*23*). Standards included permethrin at 0.1 to 0.112 kg/ha, deltamethrin at 0.008 kg/ha, fenvalerate at 0.168 kg/ha, methomyl at 1.12 kg/ha, phorate at 2.2 kg/ha, pirimicarb at 0.14 kg/ha and propargite at 0.57 kg/ha/. As seen, AC 303,630 was as good or better than the standards on all but one species at 0.125 kg/ha.

Table X: Summary of AC 303,630 vs. Standard Treatments - Comparative Results of 1988-89 Tomato, Eggplant, Potato, Celery and Sugar beet Field Trials Conducted in Brazil, Canada, Italy, the UK, and the USA

Pest (No. of trials)	AC 303,630 Rate (kg AI/ha) Providing Control >= Standard (P=.05)
Aphis fabae (1)	0.125
Helicoverpa zea (1)	0.125
Leptinotarsa decemlineata (1)	0.125
Liriomyza spp. (3)	0.125
Neoleucinodes elegantalis (1)	0.125
Phthorimaea operculella (1)	0.125
Spodoptera exigua (1)	0.125
Tetranychus urticae (1)	0.125
Keiferia lycopersicella (1)	0.250

Source: Reprinted with permission from ref. 23. Copyright 1990.

AC 303,630 is currently undergoing full scale development for use on a variety of crops and ornamentals.

Acknowledgments

The authors wish to thank J. G. Hollingshaus for establishing the uncoupling activity of dioxapyrrolomycin. The help of D. M. Gange in sorting out activity relationships based on pyrrole acidities and distribution coefficients is also gratefully acknowledged. And our thanks also go to G. Berkelhammer for his strong interest and support of this project.

Literature Cited

1. Carter, G. T.; Nietsche, J. N.; Goodman, J. J.; Torrey, M. J.; Dunne, T. S.; Borders, D. B.; Testa, R. T. *J. Antibiotics* **1987**, *40*, 233.
2. Nakamura, H.; Shiomi, K.; Iinuma, H.; Naganawa, H.; Obata, T.; Takeuchi, T.; Umezawa, H. *Ibid.* **1987**, *40*, 899.
3. Yano, K.; Oono, J.; Mogi, K.; Asaoka, T.; Nakashima, T. *Ibid.* **1987**, *40*, 961.
4. Koyama, M.; Kodama, Y.; Tsurouoka, T.; Ezaki, N.; Niwa, T.; Inouye, S. *Ibid.* **1981**, *34*, 1569.

5. Ezaki, N.; Koyama, M.; Shomura, T.; Tsuruoka, T.; Inouye, S. *Ibid.* **1983**, *36*, 1263.
6. Gonnert, R.; Schraufstäher, E. *Proc. Int. Conf. Trop. Med. Malar. 1958*, *2*, 5.
7. Saggers, D. T.; Clark, M. L.; *Nature* **1967**, *215*, 275.
8. Morton, N. *Proc. 9th British Crop Protection Conference-Pests and Diseases*, **1977**, 2, 349.
9. Nizamani, S. M.; Hollingworth, R. M. *Biochem. and Biophys. Res. Comm.* **1980**, *96*, 704.
10. Dreikorn, B. A.; O'Doherty, G. O. *Chemtech* **1985**, 424.
11. Fluazinam (Fungicide), *The Pesticide Manual* 9th Edition; Worthing, C. R.; Ed.; *Brit. Crop Protection Council*, **1991**, 402.
12. Heytler, P. G. *Phazmacol. Ther. 1980*, *10*, 461.
13. Miyoshi, H.; Fujita, T. *Biochemica et Biophysica Acta* **1988**, *935*, 312.
14. Benages, I. A.; Albonico, S. M. *J. Org. Chem. 1978*, *43*, 4723.
15. White, J.; McGillivray, G. *J. Org. Chem.* **1977**, *42*, 4248.
16. Kakushuma, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.
17. Kumar, A.; Ila, H.; Junjappa, H. *J. Chem. Soc. Chem. Comm.* **1976**, 593.
18. Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523.
19. Knot, E. B. *J. Chem. Soc.* **1947**, 1190.
20. Abdelhamid, A. O.; Negm, A. M.; Abbas, I. M. *J. Pract. Chem.* **1989**, *331*, 31.
21. Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Elsevier Biomedical Press: New York, 1986.
22. Treacy, M. F.; Miller, T. P.; Gard, I. E.; Lovell, J. B.; Wright, D. P., Jr. *Proc. Beltwide Cotton Conference* **1991**, *2*, 738.
23. Miller, T. P.; Treacy, M. F.; Gard, I. E.; Lovell, J. B.; Wright, Jr., D. P.; Addor, R. W.; Kamhi, V. M.; *Brighton Crop Protection Conf. - Pests and Diseases*, **1990**, *1*, 43.

RECEIVED March 19, 1992

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch025

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch026

Chapter 26

Insecticidal Pyrroles

Arylpyrrolecarbonitriles Incorporating a Trifluoromethyl Group

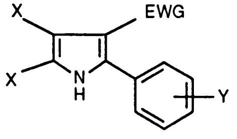
D. G. Kuhn, V. M. Kamhi, J. A. Furch, R. E. Diehl, S. H. Trotto,
G. T. Lowen, and T. J. Babcock

American Cyanamid Company, Agricultural Research Division,
P.O. Box 400, Princeton, NJ 08543-0400

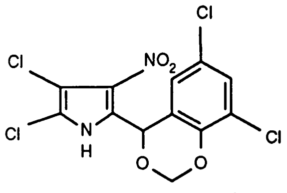
A series of new arylpyrrolecarbonitriles containing a trifluoromethyl group has been prepared. These compounds, based on a naturally occurring compound dioxapyrrolomycin, have broad spectrum insecticidal activity. This reports details the preparation of these compounds utilizing a new cycloaddition reaction. Preliminary structure-activity comparisons are also presented.

A variety of natural products have served as potential insect control agents or as "leads" for the development of synthesis programs aimed at producing structurally less complex molecules with equal or improved biological activity.

Recently, we detailed our work on the discovery of a new series of dihalopyrroles (A) having broad spectrum insecticidal activity (*1*). This series arose from our work utilizing dioxapyrrolomycin, an insecticidally active fermentation product, as a model for synthesis (*2-4*).



A



dioxapyrrolomycin

The high insecticidal activity of the 2-aryl-4,5-dihalopyrrole-3-carbonitriles (A; EWG=CN) prompted us to investigate the effect of replacement of one or both of the halogens with other groups, such as trifluoromethyl, on the biological activity (*5*).

0097–6156/92/0504–0298$06.00/0

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch026

Chemistry

Background. A convenient approach to the arylpyrrolecarbonitrile nucleus has been reported by Benages and Albonico (*6*, *7*). (Figure 1).

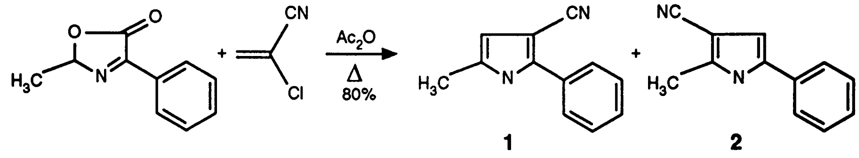


Figure 1

In this work, an oxazolinone, derived from acylated 2-phenylglycine by dehydration, adds to α-chloroacrylonitrile in a thermal cycloaddition reaction. The result is a 2:1 mixture of the regioisomeric arylpyrrolecarbonitriles **1** and **2**, respectively.

This procedure might allow for the preparation of arylpyrrolecarbonitriles substituted with a trifluoromethyl group if the corresponding trifluoromethyl substituted oxazolinones were available. In fact, these compounds have been prepared and some of their chemistry studied by Steglich and his co-workers (*8*). The oxazolinones **5** can be prepared from the corresponding amino acid derivatives **4** by a variety of procedures as shown in Figure 2.

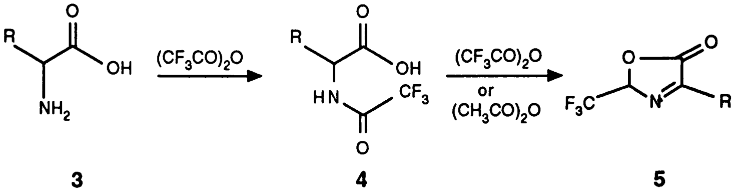


Figure 2

2-Aryl-5-trifluoromethylpyrrole-3-carbonitriles. Initial work centered on the use of the oxazolinones derived from phenylglycine or 4-chlorophenylglycine **6**. Utilizing the thermal cyclization conditions described by Albonico (*6*) with a large excess of α-chloroacrylonitrile, we obtained a low to moderate yield of the desired 2-aryl-5-trifluoromethylpyrrole-3-carbonitriles **7** as shown in Figure 3.

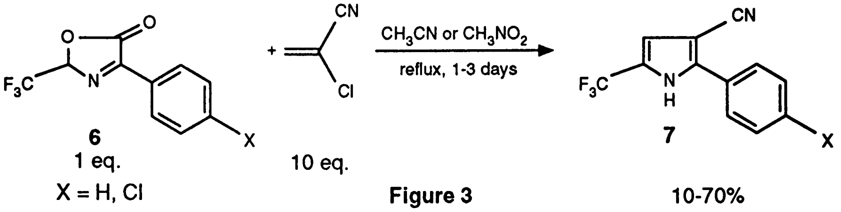


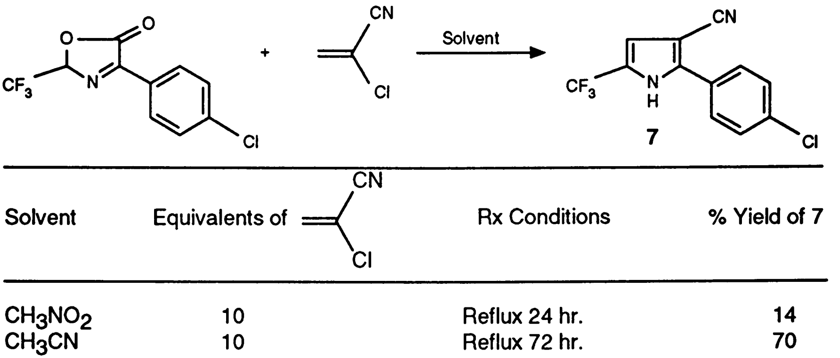
Figure 3

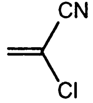
This procedure, while giving access to the desired pyrroles, was complicated by two factors. First, the large excess of α-chloroacrylonitrile used in the reaction led to the formation of polymeric material which complicated the work-up. Second, the reaction was unpredictable with regard to the time necessary to achieve maximum conversion to the pyrrole. To overcome these difficulties, a more detailed investigation of this reaction was undertaken.

It was found that the addition of one equivalent of a base to the reaction greatly reduced both the reaction time and the amount of α-chloroacrylonitrile necessary for good conversion to the pyrrole. The results are summarized in Table I. A variety of bases including triethylamine, pyridine and sodium carbonate all function in the reaction. The preferred solvents are acetonitrile or dimethylformamide. In all cases, the reaction was found to be regiospecific. Only the 2-aryl-5-(trifluoromethyl)pyrrole-3-carbonitrile regioisomer was produced.

Table I

Effects of Reaction Conditions on Yield of 7



Solvent	Equivalents of 	Rx Conditions	% Yield of 7
CH_3NO_2	10	Reflux 24 hr.	14
CH_3CN	10	Reflux 72 hr.	70
CH_3CN	1	1 eq. Et_3N Room Temperature 1 hr.	90

The scope of this base-induced pyrrole synthesis was investigated using a variety of olefins bearing electron-withdrawing groups. Some of these results are shown in Figure 4. All of the reactions were run using 1 equivalent of the olefin and 1 equivalent of triethylamine in acetonitrile at room temperature.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch026

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch026

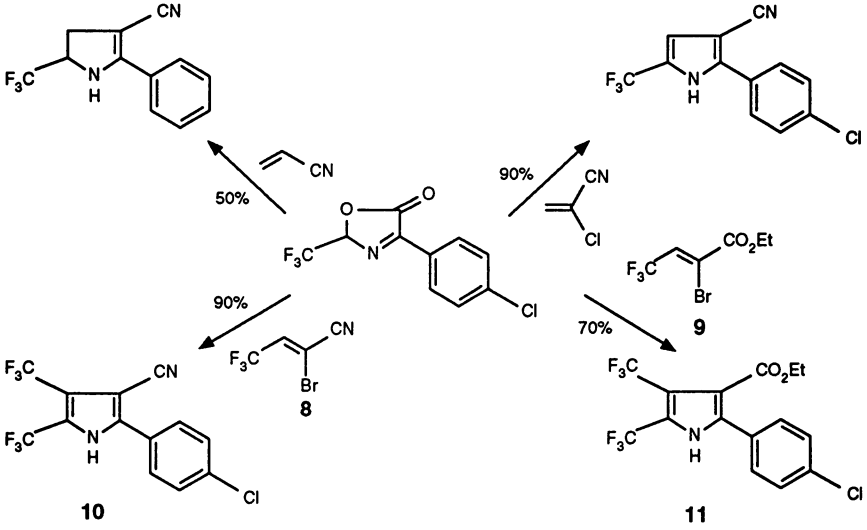

CN
F3C
N
H
50%
CN
O
O
F3C
N
Cl
90%
CN
Cl
CN
F3C
N
H
Cl
90%
CN
F3C
Br
8
F3C
CN
F3C
N
H
Cl
10
CO2Et
F3C
Br
9
70%
F3C
CO2Et
F3C
N
H
Cl
11

Figure 4

Use of α-bromotrifluorocrotononitrile **8** (*9*) or ethyl α-bromo-4,4,4-trifluorocrotonate **9** gave the 4,5-*bis*-trifluoromethylpyrroles **10** and **11** respectively. A more detailed study of this reaction will be reported separately.

Introduction of a halogen into the 4-position of the pyrrole nucleus could be accomplished using a variety of standard techniques including N-bromosuccinimide, bromine/acetic acid, or bromine/sodium acetate/acetic acid. Bromination of **7** followed by alkylation at nitrogen using chloromethyl ethyl ether gave AC 303,630 **12** which is currently in the early stages of development (Figure 5).

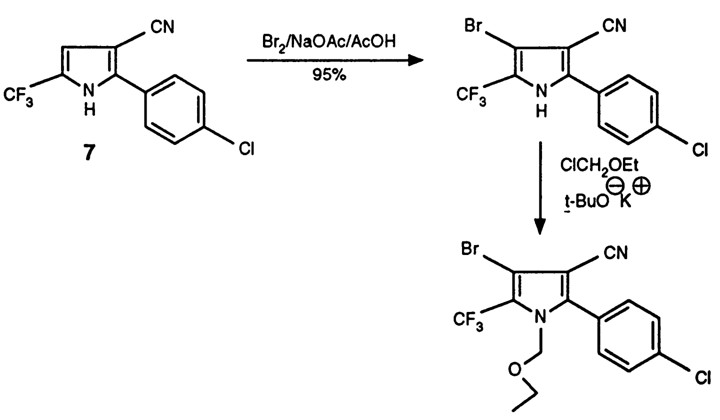

CN
CF3
N
H
7
Cl
Br2/NaOAc/AcOH
95%
Br
CN
CF3
N
H
Cl
ClCH2OEt
t-BuO⊖K⊕
Br
CN
CF3
N
O
Cl
12

Figure 5

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch026

3-Aryl-5-trifluoromethylpyrrole-2-carbonitriles. The preparation of the regioisomeric arylpyrrolecarbonitriles containing trifluoromethyl groups has been studied. Figure 6 details the synthesis of the 3-aryl-4-bromo-5-trifluoromethylpyrrole-2-carbonitrile.

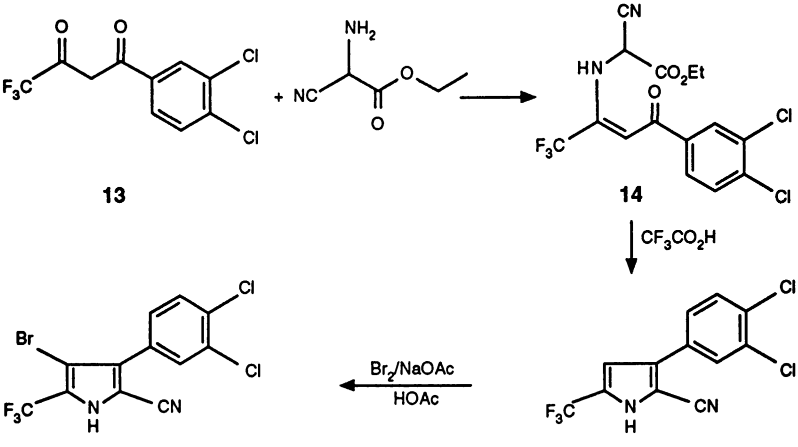


Figure 6

Treatment of the diketone **13** with ethyl α-cyanoglycinate gave the enamine **14**. Cyclization with trifluoroacetic acid followed by bromination gave the desired pyrrole **16** in excellent yield. In this procedure, purification of the intermediate pyrrole **15** was not necessary for good conversion to the final product.

Insecticidal Activity

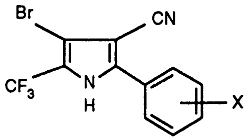
General Considerations. As was mentioned in an earlier publication (*1*), the compounds prepared in this work are capable of uncoupling oxidative phosphorylation (*10*). They are active on a variety of insect species. The chemistry developed in this work has allowed the preparation of a wide variety of analogs for structure-activity relationship studies. The insecticidal activity of two of the possible twelve positional isomers of the aryl trifluoromethylpyrrole carbonitriles is included here. The chemistry and biological activity of the remaining isomers will be reported on separately. The activity was determined using standard leaf-dip assays with technical material.

2-Aryl-4-halo-5-trifluoromethylpyrrole-3-carbonitriles. The effect of substituents on the aromatic ring on insecticidal activity is shown in Table II.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch026

Table II

Insecticidal Activity of 2-Aryl-4-Bromo-5-Trifluoromethylpyrrole-3-Carbonitriles



	% Mortality at 100 ppm			
X	Southern Army Worm Spodoptera eridania 3rd Instar	Tobacco Budworm Heliothis virescens 3rd Instar	2-Spotted Mite Tetranychus urticae P-Resistant	Western Potato Leafhopper Empoasca abrupta
H	100	100	0	0
4-Cl	100	100	100	100
4-F	100	100	0	90
4-Br	100	100	0	100
4-CF$_3$	100	100	100	100
3-Cl	100	100	0	100
3,4-Cl$_2$	100	100	100	100
2,4-Cl$_2$	100	100	100	
4-CH$_3$	100	0	0	0
4-OCH$_3$	0	0	0	60
4-OH	0	0	0	0

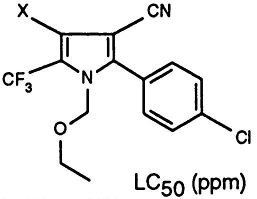
Substitution with halogen or trifluoromethyl imparts high insecticidal activity. However, alkyl, alkoxy or hydroxy groups reduce the activity. Dihalo substitution also produces active compounds. In all cases, the parent compounds were derivatized on the nitrogen to reduce any phytotoxicity observed (*1*). The presence of both the 5-trifluoromethyl group and the bromine at the 4-position was required for high insecticidal activity. However, replacement of the bromine with other halogen atoms resulted in compounds with excellent insecticidal activity. The results are summarized in Table III.

3-Aryl-4-bromo-5-trifluoromethylpyrrole-2-carbonitrile. Table IV shows a comparison of the activity between the 2-cyano series and the 3-cyano compounds described earlier. In general, the 2-cyano isomers were less active than the corresponding 3-cyano compounds either as the free NH compound or as the N-derivatized material. However, the 2-cyano compound did have good activity against leafhoppers.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch026

Table III

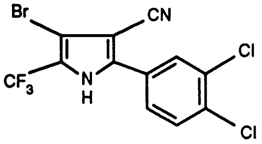
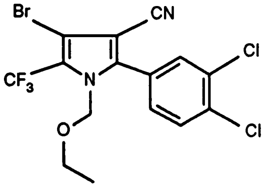
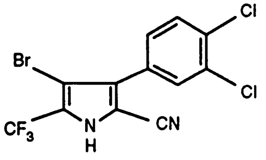
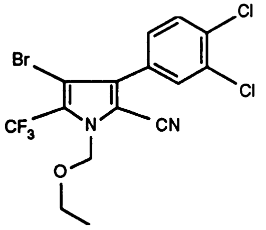
Insecticidal Activity of the 2-(4-chlorophenyl)-4-Halo-5-Trifluoromethylpyrrole-3-Carbonitriles



	LC50 (ppm)			
X	SAW	TBW	Mites	Leafhoppers
Br	4.6	7.5	2.5	0.74
Cl	3.4	9.8	7.4	0.99
I	2.9	6.3	3.2	0.55

Table IV

Activity Comparision of the 2-Aryl-4-Bromo-5-Trifluoromethylpyrrole-3-Carbonitriles and 3-Aryl-4-Bromo-5-Trifluoromethylpyrrole-2-Carbonitrile

	LC50 (ppm)			
	SAW	TBW	Mites	Leafhoppers
	2.8	6.2	<2.5	>1.0
	3.2	7.9	0.8	<10
	10.3	16	5.4	<10
	6.7	>30	>300	1.3

Conclusions

Novel arylpyrrolecarbonitriles substituted with a trifluoromethyl group have been synthesized and represent a new class of highly active insecticides. They are active against lepidopterous, piercing-sucking insects, and mites.

A new route to the 2-aryl-4-bromo-5-trifluoromethylpyrrole-3-carbonitriles has been developed. This procedure involves the base induced cycloaddition of a suitably substituted olefin to an oxazolinone containing a trifluoromethyl group. The reaction is regiospecific and gives the pyrroles in good to excellent yield.

Currently, one of these compounds, AC 303,630, is in the early stages of development.

Acknowledgments

The authors are grateful to M. Treacy, M. Miller, M. Brandolino, D. Wright, Jr. and J. Lovell for obtaining the biological data. The authors also thank Dr. D. Gange for his development of a quantitative structure-activity relationship within this series that will be reported on separately.

Finally, the authors would like to thank Dr. R. Addor for his support and continued interest in this work.

Literature Cited

1. Addor, R.; Brown, D.; Babcock, T.; Diehl, R.; Furch, J.; Kameswaran, V.; Kamhi, V.; Kremer, K.; Kuhn, D.; Siddens, J.; Treacy, M.; Trotto, S.; Wright, Jr., D., companion chapter in this volume.
2. For the isolation and identification of dioxapyrolomycin, see: Carter, G. T.; Nietsche, J. A.; Goodman, J. J.; Torey, M. J.; Dunne, T. S.; Borders, D. B.; Testa, R. T. *J. Antibiotics*, **1987**, *40*, 233.
3. Nakamura, H.; Shiomi, K.; Iinuma, H.; Naganawa, H. *J. Antibiotics*, **1987**, *40*, 899.
4. Yano, K.; Oono, J.; Mogi, K.; Asaoka, T.; Nakashima, T. *J. Antibiotics*, **1987**, *40*, 961.
5. For a discussion of the effect trifluoromethyl groups on biological activity, see: Filler, R.; Kobayashi, Y., "Biomedical Aspects of Fluorine Chemistry," Elsevier Biomedical Press, New York, N.Y. 1986.
6. Benages, I. A.; Albonico, S. M. *J. Org. Chem.*, **1978**, *43*, 4273.
7. Cardozo, M. C.; Pizzorno, M. T.; Albonico, S. M. *Tetrahedron*, **1986**, *42*, 5857.
8. Steglich, W.; Gruba, P.; Höfle, G.; Köning, W. *Angew Chem. Internal Ed.*, **1971**, *10*, 653.
9. Kuhn, D. G.; Kremer, K. A. M., U.S. Patent 5,068,390, **1991**.
10. Fukami, J.-I. *In Approaches to New Leads for Insecticides*; von Keyserlingr, H.; Jäger, A.; von Szczepanski, Ch., Eds.; Springer-Verlag: Berlin, Heidelberg, **1985**, 47-69.

RECEIVED March 19, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch026

Chapter 27

Insecticidal Pyrroles

Synthesis of Bis-(trifluoromethyl)pyrroles via Rearrangement of *O*-Vinyloximes

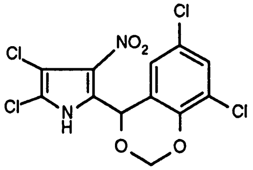
V. Kameswaran, Roger W. Addor, and R. K. Ward

Agricultural Research Division, American Cyanamid Company,
P.O. Box 400, Princeton, NJ 08543–0400

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch027

Among several synthetic strategies considered for the preparation of insecticidal pyrroles with aryl and trifluoromethyl substituents, we examined novel applications of the reported reactions of oximes and acetylenic compounds and the thermal rearrangement of the resulting vinyloximes. Rearrangements of vinyloximes **13a-e** were shown to give the targeted 4,5-*bis*-(trifluoromethyl)-pyrroles **17a-e**, respectively. In contrast to the proposed mechanism, these rearrangements were shown to proceed *via* the pyrrolin-4-ols. The 2-aryl-*bi*(trifluoromethyl)pyrroles were brominated and nitrated and also N-derivatized to give insecticidally active pyrroles.

The isolation of dioxapyrrolomycin (LL-F42248α; Figure 1) (*1-3*) from the fermentation of a culture of *Streptomyces fumanus* at the Lederle Laboratories of the American Cyanamid Company and its moderate activity against a variety of insects and mites led to the synthesis of a wide range of aryl-substituted nitro and cyano pyrroles having high broad-spectrum insecticidal and miticidal activity and is discussed in the companion chapters by Addor and coworkers and Kuhn and coworkers. Among several synthetic strategies considered for the preparation of pyrroles with substituted aryl and trifluoromethyl groups, we examined novel applications of the reported reactions of oximes and acetylenic compounds.



Dioxapyrrolomycin
Figure 1

0097–6156/92/0504–0306$06.00/0

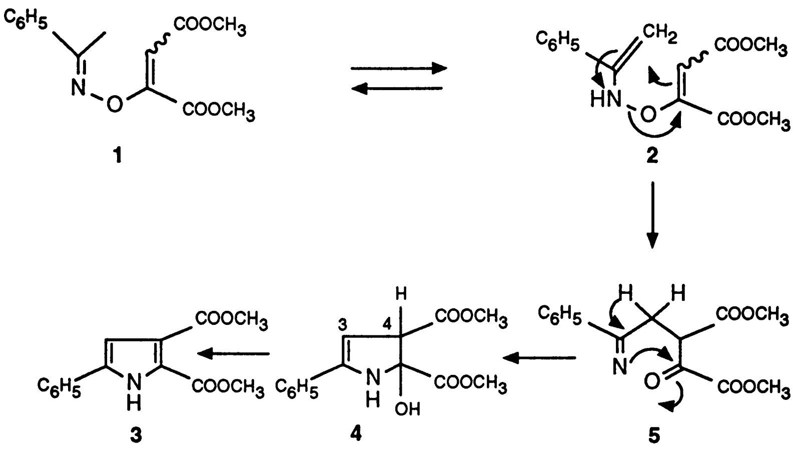
In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch027

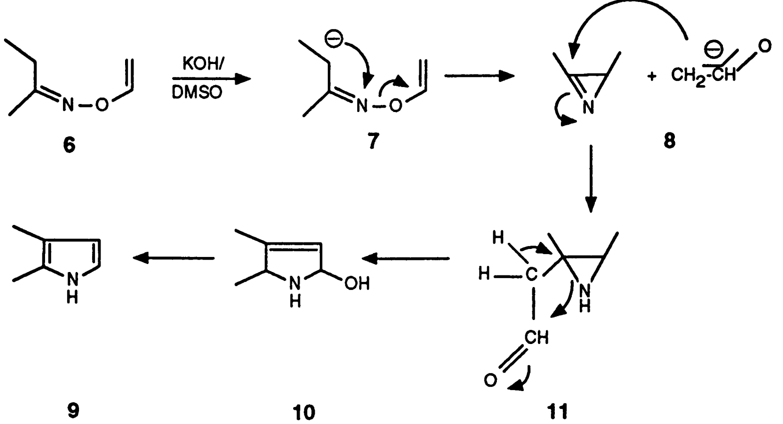
Rearrangements of Vinyloximes

Thermal rearrangement of O-vinyloxime **1** derived from acetophenone oxime and dimethylacetylene dicarboxylate has been reported by Sheradsky (*4*) to give the pyrrole derivative **3** (Scheme 1). Sheradsky's proposed mechanism involves the enamine form of the O-vinyloxime **2** which generates the C-3 to C-4 bond of the new pyrrole through a [3,3]sigmatropic rearrangement (*5-6*). Subsequent work by Trofimov et al., has used acetylene or acetylenic equivalents under strongly basic conditions to generate pyrrole derivatives (*7-10*). An azirine intermediate (*8-10*) is proposed for the reactions involving strongly basic conditions (Scheme 2). More recently, Reese (*11-12*) and co-workers have generated the required O-vinyloximes from *O*-(2-hydroxyethyl)ketoximes.

Scheme 1


C_6H_5
$COOCH_3$
N
O
$COOCH_3$
1
C_6H_5
CH_2
$COOCH_3$
HN
O
$COOCH_3$
2
C_6H_5
H
H
$COOCH_3$
N
O
$COOCH_3$
5
H
3
4
$COOCH_3$
C_6H_5
N
H
OH
$COOCH_3$
4
$COOCH_3$
C_6H_5
N
H
$COOCH_3$
3

Scheme 2


N-O
6
KOH/
DMSO
N-O
7
N
+ CH_2-CH
O
8
H
H—C
N
H
CH
O
11
N
H
OH
10
N
H
9

Results and Discussion

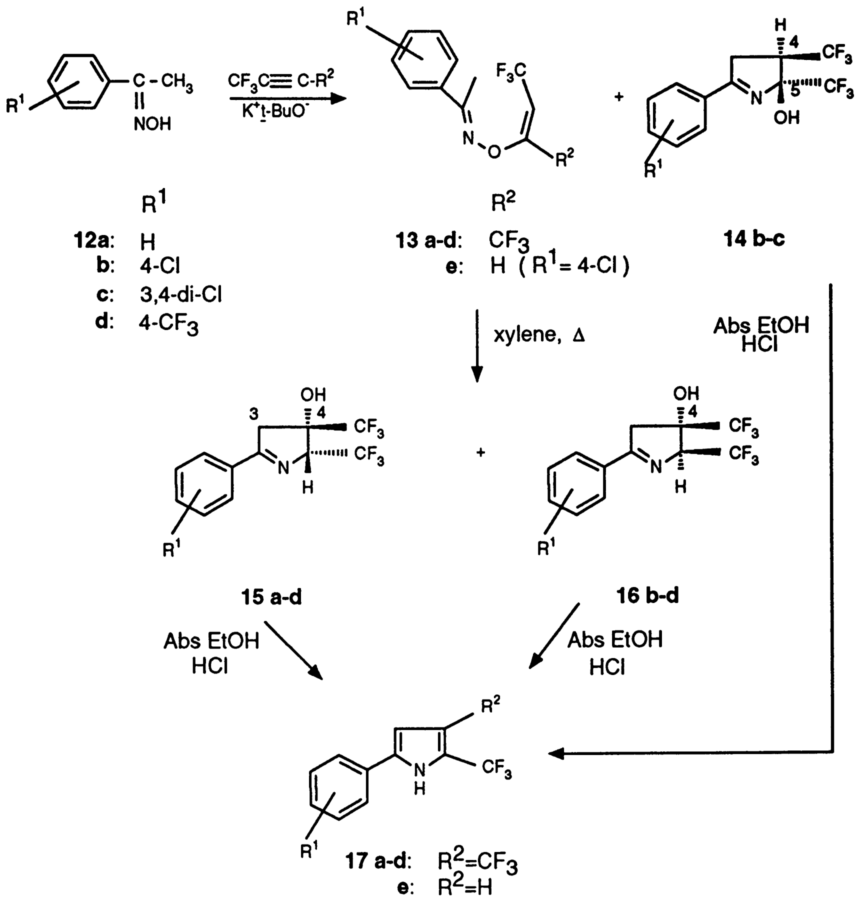
During our investigations on the synthesis of pyrroles containing trifluoromethyl group(s), we examined this vinyloxime approach using hexafluorobut-2-yne to prepare 2-aryl-4,5-*bis*(trifluoromethyl)pyrroles. Base-catalyzed reaction of acetophenone oximes **12 a-d** with hexafluorobut-2-yne using potassium *t*-butoxide in methanol gave the required O-vinyloximes **13 a-d** respectively (Scheme 3; all new compounds were analyzed by appropriate spectral data and elemental analysis). On refluxing in xylene for 4 hours, **13a** gave instead of a pyrrole a product **15a** in 43% yield which contained the elements of the expected pyrrole and a molecule of water and which on treatment with alcoholic HCl gave the 4,5-*bis*(trifluoromethyl)pyrrole **17a**. The ^{1}H NMR ($CDCl_3$) of **15a** showed an AB pattern at δ 3.51 for the C-3 methylene protons (J_{AB}=18.2 Hz) and a quartet at δ 4.88 for the C-5 methine proton (J_{HF}=7.7 Hz), indicating that the hydroxyl group was on C-4 and not on C-5, which would be expected in a possible intermediate if the [3,3] sigmatropic rearrangement as proposed by Sheradsky is operative. This unexpected observation prompted us to examine this reaction more thoroughly.

From the reaction mixture containing the O-vinyloxime **13b** (65% yield), a minor product, **14b** (7% yield) was also isolated by flash chromatography. The ^{1}H NMR (DMSO-d_6) of **14b** showed a complex multiplet at δ 3.3-3.7 for the methylene and methine protons, and the ^{13}C NMR (DMSO-d_6) showed the methine carbon at the 4-position as a quartet at δ 43.3 ($^2J_{CF}$=27.2 Hz) in the proton decoupled spectrum, thereby fixing the hydroxyl group at C-5 (for the assignment of stereochemistry, see below). This product would be the expected intermediate resulting from a [3,3] sigmatropic rearrangement of the enamine form of **13b** as proposed by Sheradsky and subsequent ring closure without the dehydration (Scheme 1). Refluxing the vinyloxime **13b** in xylene gave **15b** which crystallized out in 37% yield, and flash chromatography of the filtrate gave additional **15b**, a second dihydropyrrole **16b** (9.5% yield), and trace amounts of **14b** (Scheme 3). The ^{1}H NMR (DMSO-d_6) of **15b** and **16b** once again showed the methylene protons as an AB pattern similar to those in **15a** while the ^{13}C NMR (DMSO-d_6) showed that the methine carbon bearing the trifluoromethyl group was deshielded relative to that in **14b**, appearing at δ 75.0 ($^2J_{CF}$=27.5 Hz) and δ 79.8 ($^2J_{CF}$=28.4 Hz) respectively, thus placing the hydroxyl group on both of these structures on C-4. Their spectral similarity also indicated that they were the two possible geometric isomers. The ^{19}F-^{19}F coupling constants in their ^{19}F NMR spectra provided the necessary information to assign the stereochemistry (*13*). The *cis*-stereochemistry was assigned to **16b** due to greater ^{19}F-^{19}F coupling observed in **16b** than in **15b**. Similarly, the *trans*-stereochemistry was also assigned to the *O*-vinyloximes **13 a-e**, as no ^{19}F-^{19}F couplings were observable in the ^{19}F NMR spectra. All the three pyrrolinols were then converted to the same 4,5-*bis*(trifluoromethyl)pyrrole **17b** in almost quantitative yields with alcoholic HCl (Scheme 3). In the case of the 3,4-dichloro analog, **13c**, the two pyrrolinols, **15c** and **16c**, obtained by thermolysis were not separated, but instead the mixture was converted to the pyrrole, **17c**, with alcoholic HCl.

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch027

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch027

Scheme 3

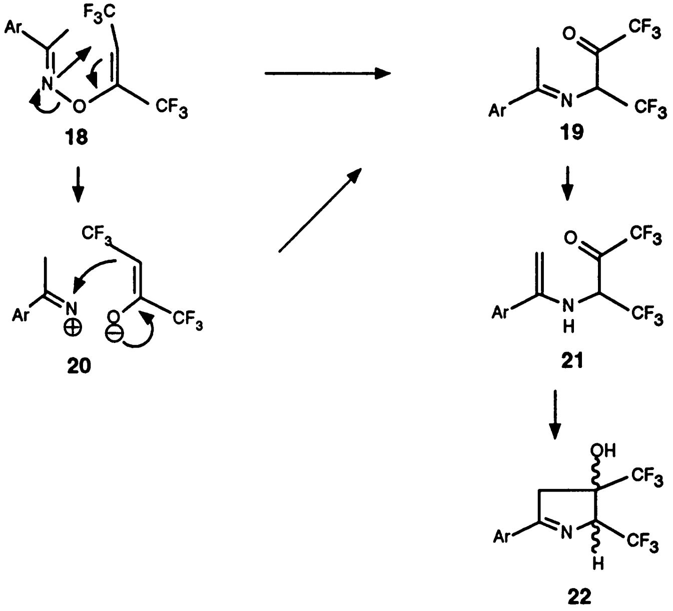

R1
C - CH3
NOH
CF3C≡C-R2
K+t-BuO-
R1
F3C
N
O
R2
+
H
4
CF3
N
5
CF3
OH
R1
R1
12a: H
b: 4-Cl
c: 3,4-di-Cl
d: 4-CF3
R2
13 a-d: CF3
e: H (R1=4-Cl)
14 b-c
xylene, Δ
Abs EtOH
HCl
OH
3
4
CF3
N
CF3
H
R1
+
OH
4
CF3
N
CF3
H
R1
15 a-d
16 b-d
Abs EtOH
HCl
Abs EtOH
HCl
R2
N
H
CF3
R1
17 a-d: R2=CF3
e: R2=H

Finally, the monotrifluoromethyl vinyloxime, **13e**, was prepared using 3,3,3-trifluoropropyne. On heating at 150-160°C, it gave directly only the 2-aryl-5-trifluoromethylpyrrole, **17e**, which was independently synthesized by another route (Lowen, G. T., unpublished results), thereby indicating that the β-carbon of vinyloxime bearing the trifluoromethyl group ends up at C-5 and not the C-4 of the pyrrole during this rearrangement.

Proposed Mechanism

The formation of pyrroles in the reaction can be accounted for by the mechanism shown on Scheme 4. In contrast to the [3,3] sigmatropic rearrangement presumably operative in Scheme 1, we propose that in the case of vinyloxime **18** an alternate [1,3] shift would provide the iminoketone **19**. A subsequent [1,3] proton shift initiates the formation of an intermediate enaminoketone **21** which readily undergoes ring closure to the pyrrolinols **22** (Scheme 4). Alternatively,

Scheme 4



the iminoketone **19** can arise by a simple heterolysis of the N-O bond in **18** to give the tight ion pair **20**, followed by recombination (Scheme 4). The formation of an azirine intermediate was, however, ruled out since such a scheme would require highly basic conditions and the regiochemistry of the resulting pyrrole would be different. Also, Nickel(II)-catalyzed synthesis of pyrroles from azirines and activated ketones has been reported (*14*) and was shown to involve the opening of the three- membered ring only at the C=N double bond, and the regiochemistry at C-2 and C-3 should be different from the present case. Experimentally, it was shown that addition of catalytic amount of *bis*(2,4-pentanedionato)nickel enabled the thermal reaction to be carried out in refluxing toluene instead of xylene, but the regiochemistry was unchanged.

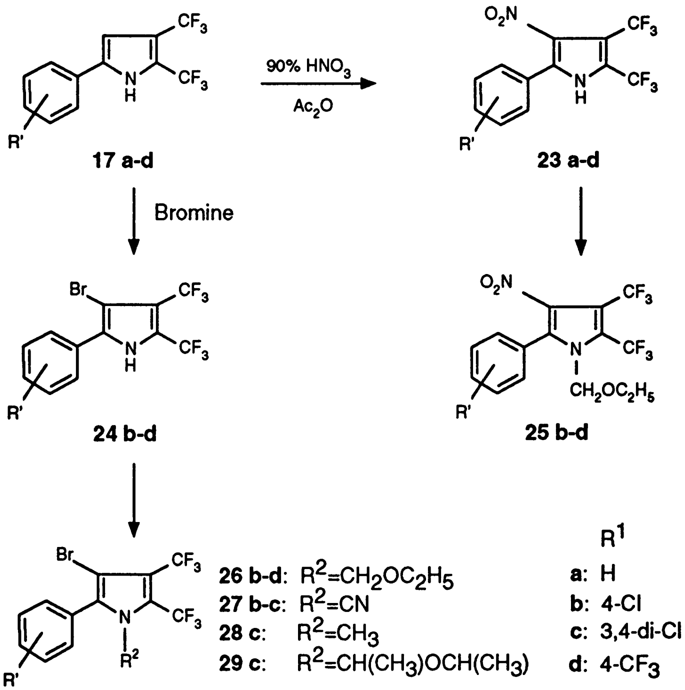
Conversions to Bromo- and Nitropyrroles

Conversion of the above *bis*(trifluoromethyl)pyrroles to the 3-cyano derivatives with the chlorosulfonyl isocyanate/dimethyl formamide procedure failed (*15*). However, they were nitrated with 90% HNO_3 in acetic anhydride to the 3-nitro derivatives and brominated with bromine and sodium acetate in acetic acid to the 3-bromo compounds (Scheme 5). A few N-derivatives were also prepared as shown in Scheme 5. These new pyrroles were found to be active in our insecticide screen. For example, compound **24c** had an LC_{50} of 1.8 ppm on third-instar tobacco budworm (Tracey, M., unpublished results).

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch027

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch027

Scheme 5



26 b-d: $R^2=CH_2OC_2H_5$
27 b-c: $R^2=CN$
28 c: $R^2=CH_3$
29 c: $R^2=CH(CH_3)OCH(CH_3)$

R^1	
a:	H
b:	4-Cl
c:	3,4-di-Cl
d:	4-CF_3

Acknowledgments

The authors wish to acknowledge the APBR Section, Agricultural Research Division, American Cyanamid Company for obtaining the mass spectral data, and the Insecticide Discovery Section for the screening data.

Literature Cited

1. Dioxapyrrolomycin was originally designated LL-F42248α: Carter, G. T.; Nietsche, J. A.; Goodman, J. J.; Torrey, M. J.; Dunne, T. S.; Borders, D. B.; Testa, R. T. *J. Antibiotics* **1987**, 40, 233.
2. Nakamura, H.; Shiomi, K.; Iinuma, H.; Naganawa, H.; Obata, T.; Takeuchi, T.; Umezawa, H.; Takeuchi, Y.; Iitaka, Y. *J. Antibiotics* **1987**, *40*, 899.
3. Yano, K.; Oono, J.; Mogi. K.; Asaoka, T.; Nakashima, T. *J. Antibiotics* **1987**, *40*, 961.
4. Sheradsky, T. *Tetrahedron Letters* **1970**, 25-26.
5. A similar mechanism is proposed for the synthesis of pyrroles from arylhydrazones and acetylenic esters; Barluenga, J.; Palacios, V.; Gotor, V. *Synthesis* **1975**, 642-643.

6. Baumes, R.; Jacquier, R.; Tarrago, G. *Bull. Soc. Chim. France* **1974**, 1147.
7. Trofimov, B. A.; Kovostova, S. E.; Mikhaleva, A. I.; Sobenina, L. N.; Vasel'wv, A. N.; Nesterneko, R. N. *Khim. Geterotsikl. Soedin.* **1983**, 273.
8. For a review on azirines in reactions involving the formation of pyrroles, see Trofimov, B. A.; Mikhaleva, A. I. *Chem. Hetero Compounds* **1987**, *23*, 1037-1049 and references cited therein.
9. For a review on reactions on ketoximes with acetylenes, see Trofimow, B. A.; Mikhaleva, A. I. *Chem. Hetero Compounds* **1980**, 979-991.
10. Korsotova, S. E.; Mikhaleva, A. I.;Sobenina, L. N.; Shevchenko, S. G.; Polovnikova, R. I. *Org. Chem. (USSR)*, **1986**, 436-438.
11. Reese, C. B.; Dhanak, D.; Romana, S.; Zappia, G. *J. Chem. Soc., Chem. Commun.* **1986**, 903-904.
12. Ellames, G. J.; Hewkin, C. T.; Jackson, R. F. W.; Smith, D. I.; Standen, S. P. *Tetrahedron Letters* **1989**, *30*, 3471.
13. Gunther, W. "*NMR Spectroscopy*", John Wiley and Sons, New York, **1980**, 350-354.
14. Faria dos Santos, F.P; Schuchardt, V. *Angew. Chem. Int. Ed.* **1977**, *16*, 647-648.
15. Loader, C. E.; Anderson, H. J. *Can. J. Chem.*, **1981**, *59*, 2673-2676.

RECEIVED March 19, 1992

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch027

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

Chapter 28

Insecticidal Dihydropyrazoles with Reduced Lipophilicity

Gary A. Meier, I. Robert Silverman, Partha S. Ray, Thomas G. Cullen, Syed F. Ali, Francis L. Marek, and Charles A. Webster

Agricultural Chemical Group, FMC Corporation, P.O. Box 8, Princeton, NJ 08543

Dihydropyrazoles are of interest as highly efficacious insecticides that do not show cross resistance with other insecticide classes. However, dihydropyrazoles are highly lipophilic molecules with potential for bioaccumulation. As part of our efforts to discover improved dihydropyrazole insecticides, we focused on modifications that would reduce the lipophilicity of the molecule while retaining the insecticidal activity. This chapter discusses synthesis, biological activity, Quantitative Structure-Activity Relationships, and relevant physical properties of these compounds.

The insecticidal properties of dihydropyrazoles have been known since the late 1970's, when workers at Philips-Duphar first described 1-carbamoyl-3-aryl-4,5-dihydropyrazoles as a promising new class of insecticide (*1,2*). They later reported that addition of a phenyl ring at the 4-position increased insecticidal activity 300-fold (*3*). Other groups have reported interesting structural variations of these compounds (*4,5,6*). Structures and insecticidal activity for select analogs representing three classes of chemistry are shown in Table I.

These compounds exhibit very good initial and residual activity against lepidoptera and in some cases, coleoptera. Because of their lipophilic nature, they have low soil and groundwater mobility. These compounds have a novel mode of action, and so do not appear to be cross resistant with other classes of insecticides.

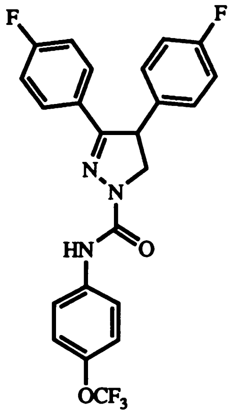
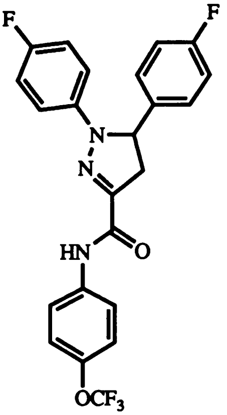
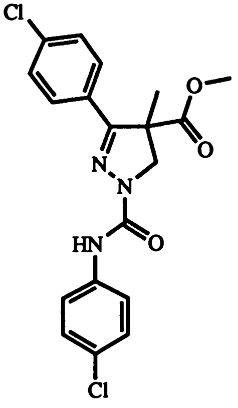
The dihydropyrazoles have been shown to cause blockage of spontaneous activity in insect sensory neurons, apparently through a voltage-dependent blockage of the sodium channel (*7*). When a dihydropyrazole such as compound **3** was injected into cockroaches, the insects became uncoordinated. Prostration and violent tremors followed. After several hours, the insects appeared to be paralyzed, but violent tremors still resulted when the insects were physically disturbed.

The dihydropyrazole insecticides have a number of shortcomings that must be overcome to make them more attractive candidates for commercialization. The compounds lack contact activity, limiting their spectrum to foliar-feeding insects. They are relatively slow acting. Test durations of 96 hours were required for best results in our insecticide screens. The compounds' high lipophilicity and metabolic stability increase their potential for bioaccumulation. Calculated Log P values (CLogP, P = n-octanol/water partition coefficient) for most dihydropyrazoles tested previously

0097–6156/92/0504–0313$06.00/0

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Table I: Dihydropyrazole Insecticide Foliar Activity

			
Compound:	1	2	3
SAW EC_{50}	0.1 ppm	4.7 ppm	2.7 ppm
MBB EC_{50}	10 ppm	75 ppm	27 ppm

SAW = southern armyworm MBB = Mexican bean beetle

fall into the range of 5 to 7. Finally, although the acute mammalian toxicity of these compounds is low, longer-term toxicity appears to be a problem. Table II shows mammalian toxicity data for F6832, one of our early experimental compounds, with a calculated Log P (CLogP) value of 5.1, and a foliar EC_{50} of 1 ppm vs. southern armyworm. Although the acute toxicity value for the compound indicates a high degree of safety, longer-term feeding studies reveal that the compound can show lethal effects at much lower doses.

Goals

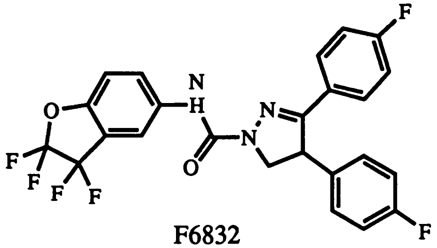
The primary goal of this project was to identify dihydropyrazole insecticides with reduced lipophilicity. We concurrently considered other means of reducing the bioaccumulation potential of these compounds, primarily the introduction of metabolically-labile groups that could be selectively cleaved in mammalian species, reducing the compound's lipophilicity, inherent toxicity, or both. A secondary goal was to search for compounds with contact activity, which could extend the utility of this class of insecticide to non-foliar feeding insects, and also improve activity against *Heliothis virescens*.

Approach

Our approach was to identify positions on the molecule where Log P-lowering substituents could be introduced, then to develop Quantitative Structure-Activity Relationship (QSAR) rules for these positions. Through application of these rules, we hoped to develop new insecticidal analogs with reduced lipophilicity and mammalian toxicity.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

Table II: Mammalian Toxicity
Oral Ingestion Studies in Female Mice



F6832

Acute LD_{50} = 760 mg/kg[a]

100% mortality within 6 days at 350 mg/kg/day[b]
100% mortality within 12 days at 100 mg/kg/day
100% mortality within 15 days at 50 mg/kg/day
80% mortality within 28 days at 33 mg/kg/day

---

[a] Single dose, study duration 14 days.

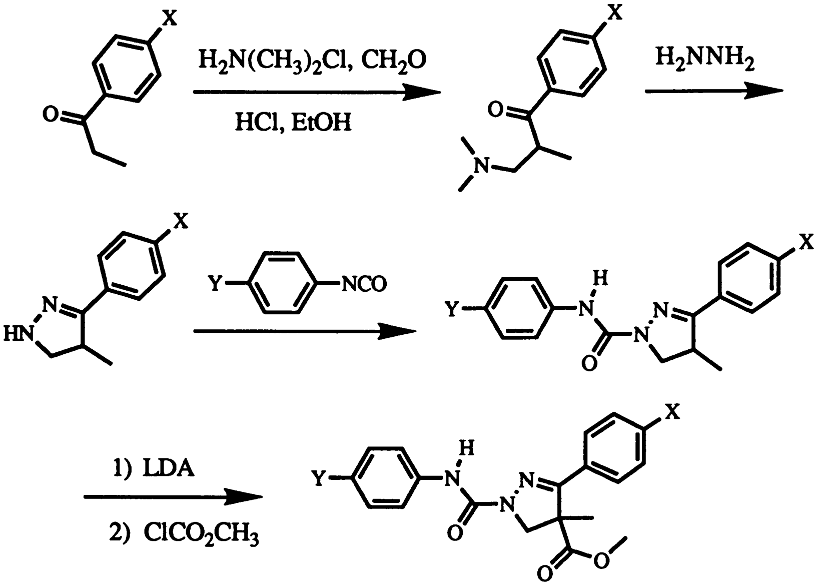
[b] Continuous feeding experiments at rate indicated.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

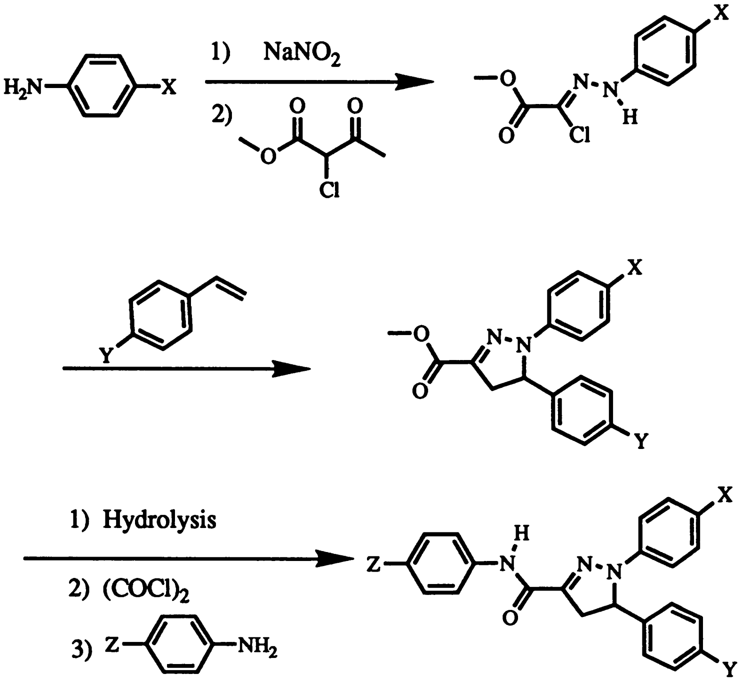
Synthesis Schemes

1-Carbamoyl-3-aryl-4-carboxymethyl-4,5-dihydropyrazoles. Details of these syntheses have been published elsewhere, and will only be briefly described here. See Scheme 1 (*5*). The aryl ethyl ketone was treated under Mannich conditions with dimethylamine hydrochloride and formaldehyde in ethanol at reflux for six hours to give, after acidic workup, the tertiary amine in 50% yield (for X = SCH_3). Treatment with aqueous hydrazine in refluxing ethanol gave quantitative conversion to the 3-aryl-4-methyl dihydropyrazole. Addition of isocyanate at room temperature to the dihydropyrazole in CH_2Cl_2 gave the 1-carbamoyl compound in 65% yield (Y = SCH_3). Deprotonating this intermediate with two equivalents of lithium diisopropylamide at -78° C, followed by addition of methyl chloroformate gave, after workup and purification, less than 10% yield of the target 1-carbamoyl-3-aryl-4-carboxymethyl-4,5-dihydropyrazole.

1,5-Diaryl-3-carbamoyl-4,5-dihydropyrazoles. Details of these syntheses have been published elsewhere, and are outlined in Scheme 2 (*6*). Briefly, the appropriately-substituted aniline in 6 N HCl was diazotized with sodium nitrite at 0°C. The diazonium salt underwent a Japp-Klingemann reaction with a solution of methyl-2-chloroacetoacetate and sodium acetate in absolute ethanol at 0°C. Warming to room temperature for two hours, followed by workup, gave the hydrazone in 65% yield (for X = Cl). The hydrazone and the appropriate styrene were mixed in toluene and heated to 90°C; after one-half hour triethylamine was added dropwise. After an additional three hours of heating, workup gave the 3-carbomethoxy dihydropyrazole in 54% yield (Y = Cl). Hydrolysis in refluxing methanolic NaOH gave the carboxylic acid in 90% yield. The acid chloride was prepared using oxalyl chloride/dimethylformamide (DMF) in toluene. Solvent was removed *in vacuo*, and the crude material was dissolved in


X
$H_2N(CH_3)_2Cl$, CH_2O
HCl, EtOH
O
N
H_2NNH_2
HN
N
Y
NCO
H
1) LDA
2) $ClCO_2CH_3$

Scheme 1: Synthesis of 1-Carbamoyl-3-aryl-4-carboxymethyl-4,5-dihydropyrazoles.

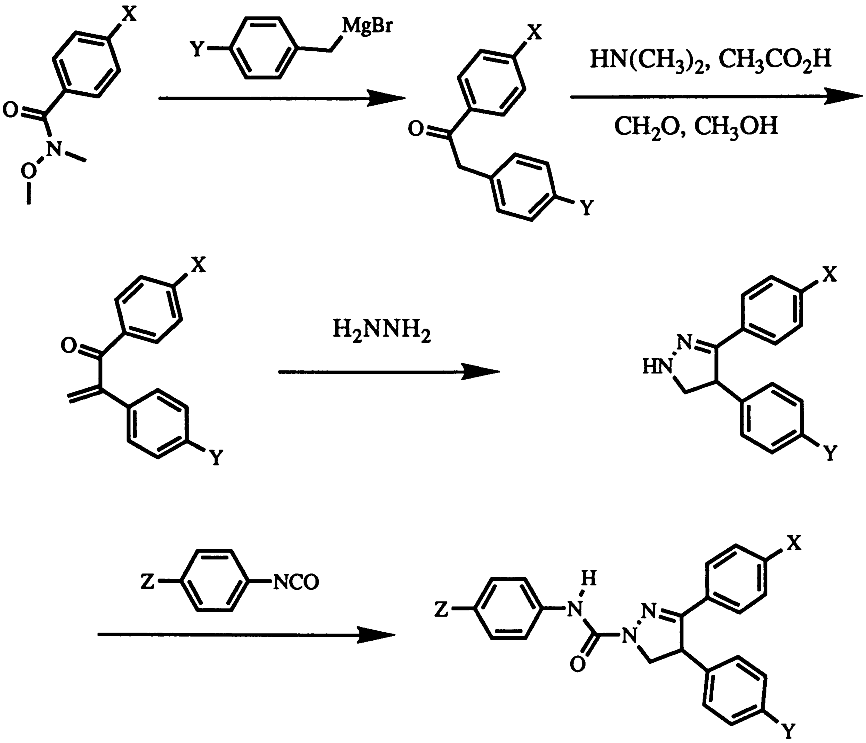

H_2N
X
1) $NaNO_2$
2)
O
Cl
N
H
Y
1) Hydrolysis
2) $(COCl)_2$
3) Z
NH_2

Scheme 2: Synthesis of 1,5-Diaryl-3-carbamoyl-4,5-dihydropyrazoles.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

tetrahydrofuran (THF). A solution of the aniline and triethylamine in toluene was added at room temperature, and after two hours the reaction was worked up to give the 1,5-diaryl-3-carbamoyl-4,5-dihydropyrazole target in 41% yield (Z = Cl).

1-Carbamoyl-3,4-diaryl-4,5-dihydropyrazoles. Details of these syntheses have been published, and are outlined in Scheme 3 (*3,8*). Several suitable routes exist for preparation of the ethanone intermediate, including addition of the benzyl Grignard reagent to the N-methyl-N-methoxybenzamide, as shown. A Mannich reaction with the ethanone, formalin, dimethylamine and acetic acid in refluxing methanol gave the α,β-unsaturated ketone in nearly quantitative yield (when X = Y = F). This intermediate was dissolved in ethanol, treated with aqueous hydrazine at room temperature, then heated to reflux for one hour. Workup gave the 3,4-diaryl-4,5-dihydropyrazole in 96% yield. This intermediate was generally not isolated, but rather added in ether solution to the appropriate aryl isocyanate at room temperature to give the target 1-carbamoyl-3,4-diaryl-4,5-dihydropyrazole in 60% yield (Z = I).



Scheme 3: Synthesis of 1-Carbamoyl-3,4-diaryl-4,5-dihydropyrazoles.

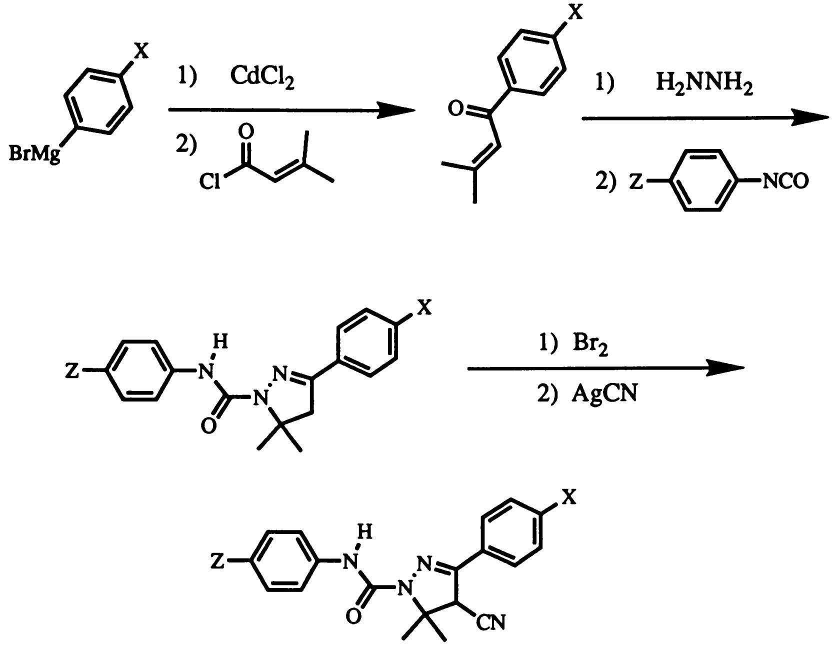
1-Carbamoyl-3-aryl-4,5-dihydropyrazoles with Log P-lowering substituents in the 4-position.

4-CN-dihydropyrazoles. Scheme 4 outlines the synthesis of dihydropyrazoles with a nitrile substituent in the 4-position. The appropriate aryl Grignard reagent (0.2 mol) in ether was treated with solid $CdCl_2$ (0.1 mol) and stirred under a nitrogen

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

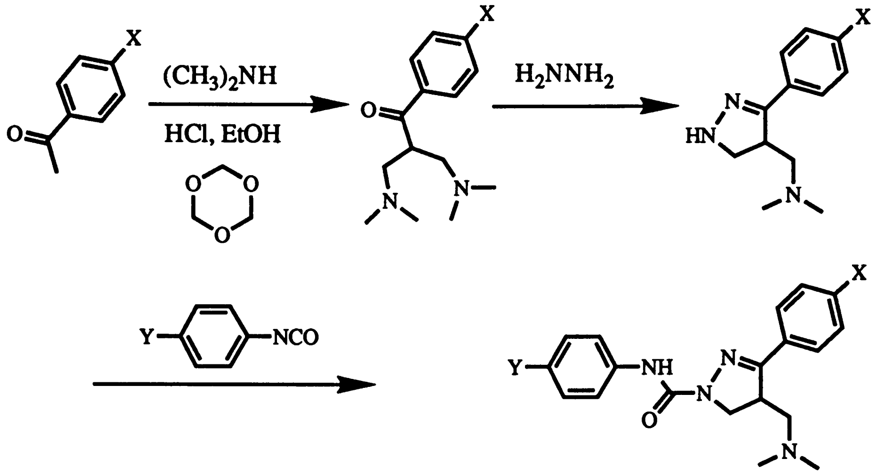
atmosphere. The mixture was refluxed for one and one-half hours, allowing much of the ether to evaporate. The reaction was then cooled to room temperature and dry toluene was added followed by 3,3-dimethylacryloyl chloride (0.2 mol) in toluene. The reaction was refluxed for 14 hours, stirred at room temperature for two days, then quenched with 20% H_2SO_4 (aq.) and extracted with toluene. Yield of the α,β-unsaturated ketone was 71% after distillation (X = F). The ketone was mixed with a slight excess of hydrazine hydrate in n-propanol and refluxed for four hours, then stored at 0°C overnight. Removal of solvent *in vacuo* gave high yield of crude dihydropyrazole, which was dissolved in CH_2Cl_2 and treated at room temperature with one equivalent of aryl isocyanate. Removing solvent *in vacuo* after 2.5 hours gave the 1-carbamoyl-3-aryl-dihydropyrazole in 87% yield (Z = F). This intermediate was dissolved in CCl_4 and treated with one equivalent of Br_2. The solution was refluxed for two hours, then stirred at room temperature overnight. Removal of solvent gave the 1-carbamoyl-3-aryl-4-bromo dihydropyrazole in quantitative yield. The 4-bromo intermediate was dissolved in CH_3CN and treated with a slight excess of AgCN. Heating to 60°C for two hours gave the target 4-CN dihydropyrazole in 28% yield after recrystallization.



Scheme 4: Synthesis of 1-Carbamoyl-3-aryl-4-cyano Dihydropyrazoles.

4-Methyl(dimethylamino) dihydropyrazoles. See Scheme 5. Reaction of the appropriately-substituted acetophenone with dimethylamine hydrochloride, concentrated HCl, and trioxane in ethanol gave the bis-methyl(dimethylamino) intermediate in 34% yield (when X = F). This was treated with hydrazine hydrate as described above to yield the 4-methyl(dimethylamino) dihydropyrazole, which was

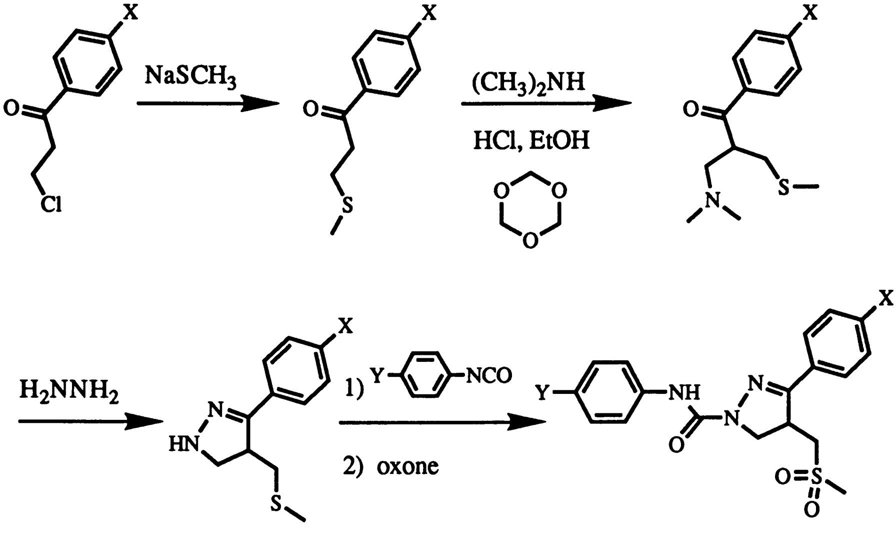
Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028


X
O
$(CH_3)_2NH$
HCl, EtOH
O O O
N
N
H_2NNH_2
N
HN
N
Y
NCO
NH
N
O

Scheme 5: Synthesis of 3-Aryl-4-methyl(dimethylamino) Dihydropyrazoles.

typically not isolated, but treated with the aryl isocyanate to give the target 1-carbamoyl-3-aryl-4-methyl(dimethylamino) dihydropyrazole in 36% yield (Y = OCF_3) from the bis-methyl(dimethylamino) intermediate.

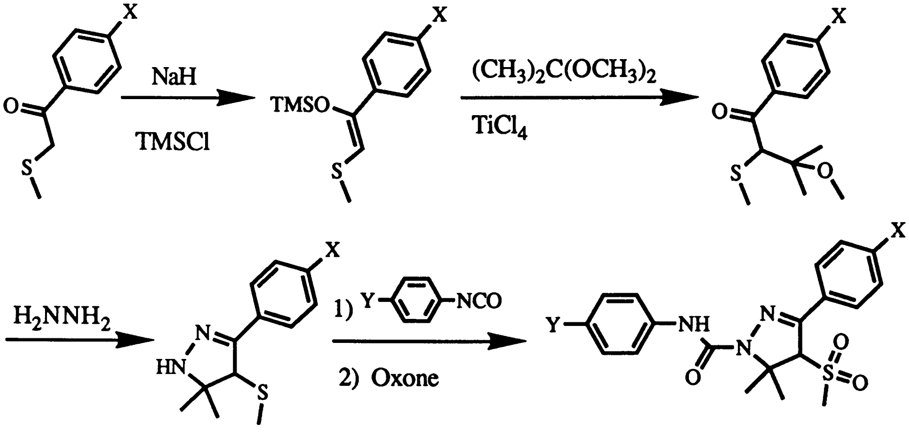
4-Methyl(methylsulfonyl) dihydropyrazoles. See Scheme 6. The 3-chloropropiophenone was treated with $NaSCH_3$ in methanol at room temperature to give the thioether in quantitative yield (X = F). The thioether was reacted under the Mannich conditions described above to give a complex mixture, containing the indicated


X
O
Cl
$NaSCH_3$
S
$(CH_3)_2NH$
HCl, EtOH
O O O
N
S
H_2NNH_2
N
HN
S
1) Y NCO
2) oxone
Y
NH
N
O
O=S
O

Scheme 6: Synthesis of 3-Aryl-4-methyl(methylsulfonyl) Dihydropyrazoles.

3-dimethylaminopropiophenone. This mixture was treated with hydrazine hydrate to give a low yield of the 4-methyl(methylsulfide) dihydropyrazole which was not isolated, but treated directly with the appropriate aryl isocyanate to give the 1-carbamoyl-3-aryl-4-methyl(methylsulfide)-3,4-dihydropyrazole in low yield. Oxidation of the sulfide under Trost's conditions (oxone in methanol) gave the sulfone target in 75% yield (9).

Synthesis of 4-methylsulfonyl dihydropyrazoles. See Scheme 7. The S-methyl acetophenone was deprotonated with NaH in THF at 0°C and treated with trimethylsilyl chloride (TMSCl) to yield the TMS-protected enol ether in 36% yield (for X = F). A Mukaiyama-type reaction ($TiCl_4$, 2,2-dimethoxypropane in CH_2Cl_2 at -78°C) gave the aldol product in 55% yield (10). Treatment with hydrazine hydrate in propanol at 80°C gave the dihydropyrazole in 43% yield. Reaction with the aryl isocyanate in refluxing CH_2Cl_2 gave the 1-carbamoyl-3-aryl-4-thiomethoxy dihydropyrazole in 42% yield (Y = CN). This was oxidized as in the previous scheme with oxone in MeOH to yield the target 1-carbamoyl-3-aryl-4-methylsulfonyl dihydropyrazole in 41% yield (9).



Scheme 7: Synthesis of 4-Methylsulfonyl Dihydropyrazoles.

Biological Testing

The compounds were screened for insecticidal activity against southern armyworm (*Spodoptera eridania*), tobacco budworm (*Heliothis virescens*), and Mexican bean beetle (*Epilachna varivestis*).

The activity of the test compounds was determined by spraying the upper and lower surfaces the leaves of pinto bean plants (*Phaseolus vulgaris*) with test solution until run-off and infesting with first instar larvae (ten larvae for each of two replicates for each compound) after the foliage had dried.

To prevent escape of the insects from the test site, the treated plant or excised leaves were placed in capped cups. The tests were held at 25°C and 50% relative humidity for an exposure period of 96 hours. At the end of this time, percent mortality was determined and EC_{50} values were determined by probit analysis.

Efficacy in residual testing was determined by spraying the test plants to run-off with aqueous dilutions of the compounds. The treated plants were held under

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

greenhouse conditions for the appropriate period of time before infestation with insects. The test was then completed as described for the initial evaluations.

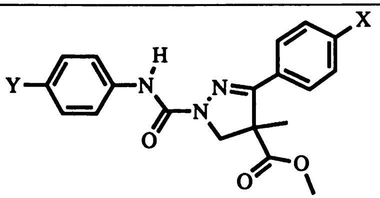
Acute oral toxicity to mice was determined by feeding groups of five female B6C3F1 mice graded dosages of a 10% weight/volume suspension of the experimental compound in corn oil. Observations for toxicity were made periodically for 14 days. Animals surviving the full 14 days appeared normal when necropsied. Subchronic oral toxicity was determined in a similar manner, with graded dosages of the experimental compound administered daily to groups of five female mice for up to 28 days.

CLogP values were determined from an additive model using Medchem software (Version 3.33, Leo, A., and Weiniger, D. Pomona College). This software is not fully parameterized for the dihydropyrazole ring; therefore, the values reported here are useful only for comparisons between compounds in a given class of chemistry. Experimental Log P estimations were made by reverse-phase high-performance liquid chromatography. The retention time of each experimental compound, corrected for the dead volume of the system, was compared to a calibration curve prepared by regression analysis of the retention times for a set of 10 standards with Log P values ranging from 0.8 to 7.3.

Results and Discussion

The 1-carbamoyl-3-aryl-4-carbomethoxy dihydropyrazoles were investigated first. It is known that the pyrazole analogs of the dihydropyrazoles generally do not possess insecticidal activity. In the 4-carbomethoxy dihydropyrazole series, therefore, a suitable blocking group was required to prevent β-elimination which would convert the dihydropyrazole ring to the corresponding pyrazole. A methyl group in the 4-position is generally used for this purpose. Unfortunately, the 4-carbomethoxy-4-methyl analogs are essentially as lipophilic as the 3,4-diaryl dihydropyrazoles, such as F6832 in Table II. Table III shows the biological activity of several analogs in the 4-carbomethoxy series, including one low Log P analog (CLogP = 0.8) in which X = Y = $S(O)_2CH_3$. While lipophilic analogs bearing halogen or trifluoromethyl substituents in these positions show good to excellent foliar activity against southern armyworm, the

Table III: Foliar Activity of 1-Carbamoyl-3-aryl-4-carbomethoxy Dihydropyrazoles



X	Y	Southern Armyworm Foliar EC_{50} (ppm)	CLogP
Cl	Cl	3	5.5
Cl	CF_3	17	5.7
CF_3	Cl	7	5.7
SCH_3	SCH_3	inactive	5.2
$S(O)_2CH_3$	$S(O)_2CH_3$	inactive	0.8

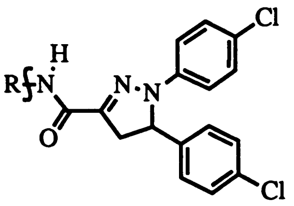
Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

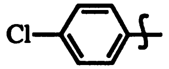
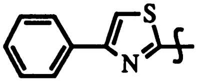
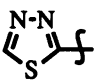
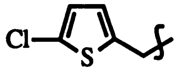
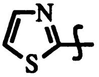
Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

methylsulfonyl analog was inactive at a rate of 100 ppm. The synthetic precursor (X = Y = SCH_3) of the methylsulfonyl analog was also tested and found to be inactive, but it is not known if the thiomethyl groups are inherently inactive or if they are being oxidized to methylsulfonyl groups *in vivo*..

A slightly different approach was taken in the 1,5-diaryl-3-carbamoyl dihydropyrazole series. Rather than introduce Log P-lowering substituents onto the aromatic rings, various heteroaryl groups were introduced into the 3-carbamoyl moiety (Table IV). The thiadiazole showed the greatest drop, of 1.3 Log P units relative to the 4 chlorophenyl substituent chosen as a reference. Nevertheless, with a CLogP value of 4.6, the thiadiazole compound remains fairly lipophilic. More importantly, the biological activity was significantly reduced in all of the compounds in which the carbamoyl phenyl ring was replaced by a heteroaryl group.

Table IV: Foliar Activity of 1,5-Diaryl-3-carbamoyl Dihydropyrazoles



R	Southern Armyworm Foliar EC_{50} (ppm) or % control at 100 ppm	CLogP
	27 ppm	5.9
	13% at 100 ppm	6.6
	13% at 100 ppm	4.6
	inactive	5.6
	inactive	4.9

Because the 1-carbamoyl-3-4-diaryl-4,5-tetrahydropyrazoles tended to show better insecticidal activity than the 1,5-diaryl-3-carbamoyl or the 1-carbamoyl-3-aryl-4-carbomethoxy analogs, we turned to this class of chemistry to begin our QSAR analysis. Table V shows the training set synthesized to study the 4-position of the 1-carbamoyl phenyl ring. Physicochemical parameters for the substituents were obtained from literature sources or calculated, and statistical analyses were carried out using BMDP software (Dixson, W. J. BMDP Statistical Software; University of

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

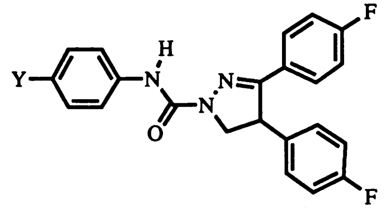
California, Berkeley 1983). Biological activity for southern armyworm foliar testing was expressed in $P(EC_{50})$ units, related to the foliar EC_{50} by the equation $P(EC_{50}) = -\log(EC_{50}/MW \times 1000)$ where MW is the molecular weight of the compound. Regression analysis provided equation 1.

$$P(EC_{50}) = 6.88 + 0.45\ (+/-\ 0.15)\ \pi + 1.54\ (+/-\ 0.30)\ \sigma - 0.59\ (+/-\ 0.21)\ L \qquad (1)$$
$$n = 12 \quad r = 0.90 \quad s = 0.56 \quad F = 11.42\ (p = 0.003)$$

Equation 1 explains the observed data reasonably well, correlating insecticidal activity with the Y substituent's lipophilicity (π) and electron withdrawing character (σ), and showing a negative correlation between insecticidal activity and the sterimol length parameter (L), where L is the length of the substituent along the axis of substitution to the aromatic ring. The correlation matrices showed little or no cross-correlation between π, σ, and L. Development of the equation showed that no single variable accounted for more than 50% of the observed bioactivity ($r^2 < 0.50$), while no combination of two variables accounted for more than 62% of the bioactivity (Silverman, I. R, et al. manuscript in preparation). Having established a positive correlation between biological activity and lipophilicity of the substituent in the 4-position of the carbamoyl phenyl, the 4-position of the 4,5-dihydropyrazole ring was next considered for QSAR analysis. The training set shown in Table VI was synthesized and tested for southern armyworm activity. The regression analysis was performed as above, yielding equation 2.

$$P(EC_{50}) = 3.70 + 1.74\ (+/-\ 0.58)\ \sigma^* + 0.44\ (+/-\ 0.13)\ L - 0.37\ (+/-\ 0.11)\ B4 \qquad (2)$$
$$n = 15 \quad r = 0.85 \quad s = 0.62 \quad F = 9.22\ (p = 0.002)$$

Table V: QSAR Set for 1-Carbamoyl Position



Y	EC_{50} (ppm)	Southern Armyworm Foliar Data	
		$P(EC_{50})$	Predicted $P(EC_{50})^a$
CF_3	0.1	6.87	6.16
Br	0.4	6.06	5.36
NO_2	0.5	5.72	5.93
CN	10	4.60	5.14
SCH_3	13	4.51	4.62
$S(O)CH_3$	12	4.56	4.54
$S(O)_2CH_3$	12	4.58	4.68
t-Bu	40	4.03	5.04
$NHC(O)CH_3$	90	3.68	3.41
NH_2	107	3.56	3.58
$N(CH_3)_2$	120	3.53	3.60
$N(C_3H_7)_2$	170	3.45	3.20

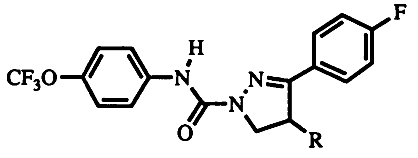
[a] From Equation 1.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

Equation 2 was considerably more promising. Insecticidal activity correlated to the R group's σ^* value (the electron withdrawing character for a substituent on an aliphatic position) and its length (L), and showed a negative correlation with B4, the substituent's radius measured 180°C away from the substituent's minimum radius (B4 is usually the substituent's maximum radius, as measured perpendicular to the axis L). The correlation matrix showed these parameters to be well separated. Development of the equation showed that no single variable accounted for more than 25% of the observed bioactivity ($r^2 < 0.25$), while no combination of two variables accounted for more than 58% of the bioactivity (Silverman, I. R, et al. manuscript in preparation). Lipophilicity in this position was not correlated with bioactivity, which allowed us to propose new analogs with Log P-lowering substituents in the 4-position.

Table VII shows several of the structures we proposed and synthesized as potential dihydropyrazole insecticides with reduced lipophilicity. All were predicted by the QSAR equation to have good insecticidal activity, although the substituents selected were outside the range of physicochemical parameters covered by the training set in Table VI. Log P values for these compounds were significantly reduced relative to dihydropyrazoles such as **1**, **2**, and **3**, despite the presence of the gem-dimethyl blocking groups introduced into the 5-position of the dihydropyrazole ring to prevent aromatization in the case of the 4-CN and 4-SO_2CH_3 compounds. Most of these compounds, unfortunately, had little or no insecticidal activity. The exception, and most promising compound to come out of this work, was the 4-methyl-(dimethylamino) analog, Compound **4**, shown in Table VII. This compound has a remarkably low CLogP value for a dihydropyrazole insecticide and retains reasonable insecticidal activity.

Table VI: QSAR Set for Dihydropyrazole 4-Position

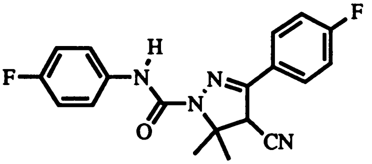
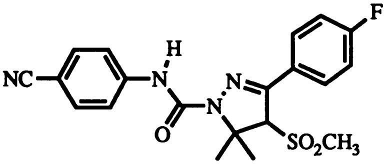
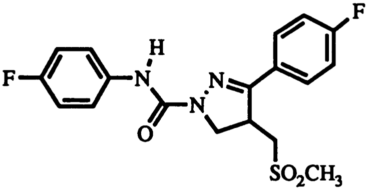
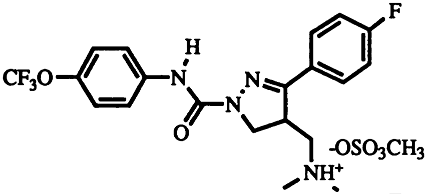
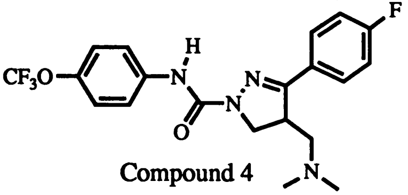


R	Southern Armyworm Foliar Data EC_{50} (ppm)	$P(EC_{50})$	Predicted $P(EC_{50})^a$
4-fluorophenyl	0.1	6.72	6.54
phenyl	0.1	6.65	6.21
propyl	1.5	5.44	4.45
pentyl	2.3	5.28	4.80
$CH_2N(CH_3)_2$	7.0	4.78	4.84
isobutyl	8.0	4.72	4.11
$(CH_2)_2SO_2CH_3$	21	4.42	4.83
cyclopropyl	18	4.35	4.21
$(CH_2)_3OCH_3$	20	4.34	5.00
ethyl	19	4.32	4.22
cyclopentyl	30	4.16	4.07
cyclohexyl	75	3.78	4.98
benzyl	110	3.62	3.55
methyl	130	3.47	4.20
4-methoxybenzyl	260	3.27	3.31

[a] From Equation 2.

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

Table VII: 1-Carbamoyl-3-aryl Dihydropyrazoles with Reduced Lipophilicity

Compound	Southern Armyworm Foliar EC_{50} (ppm) or % control at 100 ppm	Log P
	inactive	3.5
	inactive	2.3
	inactive	2.4
	30%	—
 Compound 4	EC_{50} = 7 ppm	4.2[a]

[a] CLogP value

Conclusions

The dihydropyrazoles hold great promise as potential insecticides if the problems of potential bioaccumulation and mammalian toxicity can be overcome. With this goal in mind, we initiated a search for dihydropyrazole insecticides with reduced lipophilicity. QSAR analysis indicated that insecticidal activity of the 1-carbamoyl-3,4-diaryl-4,5-dihydropyrazoles was positively correlated to the lipophilicity of the substituent in the 4-position of the carbamoyl phenyl ring. However, a QSAR study on the 4-position of the dihydropyrazole ring indicated that bioactivity was correlated to the σ*, L, and B4 parameters of the substituent at this position, but not to lipophilicity (Equation 2). A set of compounds containing substituents in the 4-position with favorable σ^*, L, and B4 parameters and Log P-lowering character was prepared and tested (Table VII). The physicochemical parameters for substituents in this set were generally outside the range of parameters used in developing Equation 2, and biological evaluation showed most of the compounds in this set to have little or no insecticidal activity. However, compound **4** in Table VII did show reasonable insecticidal activity, with a southern armyworm foliar EC_{50} of 7 ppm and a CLogP value 1-2 Log P units below the values for most of the dihydropyrazoles we had tested prior to initiation of this project. At this time, the mammalian toxicity of compound **4** has not been evaluated.

Acknowledgments

The authors thank Steve Szczepanski, John Longo, Saroj Sehgel, Joan Rachubinski, and Joan Buote for their assistance in the synthesis of some of the compounds discussed here, as well as Christine Freeman, Jane McCarty and Don Nye for providing the mammalian toxicity data. Thanks also to Jim Willut for carrying out the experimental Log P determinations, and to Angelina Duggan and Ernest Plummer for valuable discussions. Finally, the authors acknowledge the support of FMC Corporation.

Literature Cited

1. Mulder, R., Wellinga, K., van Daalen, J. J. *Naturwissenschaften*, **1975**, *62*, 531.
2. Wellinga, K., Grosscurt, A. C., van Hes, R., *J. Agric. Food Chem.* **1977**, *25*, 988.
3. Grosscurt, A. C., van Hes, R., Wellinga, K. *J. Agric. Food Chem.* **1979**, *27*, pp 406-409.
4. Jacobson, R. M., U.S. Patent 4,663,341, **1987**
5. Jacobson, R. M. *Recent Advances in the Chemistry of Insect Control*, Crombie, L., Ed.; The Royal Society of Chemistry: London, **1989**; pp 206-211.
6. Stevenson, T. M., PCT Application WO 88/06583, **1988**
7. Salgado, V. L. *Pesticide Science*. **1990**, *28*, 389-411.
8. Duggan, A. J., U.S. Patent 4,767,779, **1988**
9. Trost, B. M., Curran, D. P. *Tet. Lett.* **1981**, *22*, 1287.
10. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, pp 817-826.

RECEIVED July 6, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch028

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029

Chapter 29

N-Benzoyl-*N*-alkyl-2-aminothiazole Proinsecticides

Marty C. Wilkes[1], Paul B. Lavrik, and John Greenplate

Monsanto Agricultural Products Company, 700 Chesterfield Village Parkway, St. Louis, MO 63198

When a series of seventeen N-benzoyl-2-amino-5-chloro-4-trifluoromethylthiazole amides were prepared and screened as potential *Heliothis virescens* (tobacco budworm) (TBW)) insecticides, an N-methyl group at the amide nitrogen eliminated phytotoxicity and reduced acute rat toxicity. Subsequently, the effect of deuterium incorporation in the N-methyl group on TBW mortality was investigated. The NCD_3 derivative was inactive while the NCH_3 derivative exhibited a diet incorporation LC_{50} of 109 ppm (+/- 20 ppm) against TBW suggesting a deuterium isotope effect in abstraction of the methyl hydrogen atoms by cytochrome P-450 enzymes.

Two market forces drive industrial pesticide research progress supply and demand. On the demand side, the need for new classes of environmentally acceptable pesticides is increasing. On the supply side, existing pesticides are being removed from the market for selectivity and resistance reasons. In searching for new classes of agrochemicals such as insecticides, nonselective toxins are relatively easily discovered (*1*). The general problem is whether there is any systematic way to improve these toxins' selectivity patterns and restrict their lethality to the target pest by taking advantage of metabolic pathways in the target (*2*). While this approach of selectivity "clean up" remains largely a dream, limited steps can be taken in this direction.

In the course of screening for classes of chemical insecticides we discovered a class of amides **1** shown below in Figure 1. When R=H

---

[1] **Current address: Warner-Jenkinson Company, 2526 Baldwin Street, St. Louis, MO 63178–4538**

0097–6156/92/0504–0327$06.00/0

compound **1a** exhibited a tobacco budworm (TBW) LC_{50} of 1-10 ppm via diet incorporation. Unfortunately these compounds were phytotoxic and exhibited rat toxicity effects.

Our approach to this problem was to vary the substituent R to create a series of potential propesticides (*3*). We introduced various substituents at the R group that would be readily removed by the insect and create a pesticide in situ. We hoped to take advantage of the relatively rapid metabolism rate of insects relative to other organisms in the process. Secondly, we developed a new in vivo method of actually demonstrating that these propesticides were in fact converted to the pesticide in the insect and we chose to use deuterium isotope effects for this demonstration.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029

Synthesis of N-Benzoyl-N-Alkyl-2-Aminothiazoles

Figure 2 below displays our most generally applicable route to the desired thiazole propesticides (*4*). Beginning with the traditional Hantzch thiazole synthesis (*5*) we condensed 1,1,1-trifluoro-3-bromo-2-propanone with an alkylthiourea in refluxing water to obtain the hydrobromide salt of the aminothiazole **3** and the resulting mixture was extracted with sodium hydroxide to give the free amine in moderate to excellent yield depending on the R substituent.

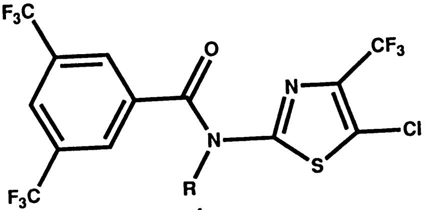
Aminothiazoles **3** in turn were selectively chlorinated in the 5-position with N-chlorosuccinimide in refluxing acetonitrile to obtain the 5-chlorothiazole **2** in moderate to excellent yield. Finally **2** was condensed with an acid chloride to obtain the amides **1** in moderate to excellent yields depending on the substituents present. This synthesis worked quite well for simple R groups such as hydrogen, ethyl, isopropyl, methoxy, benzyl, and phenyl type substituents.

However, in cases where the byproduct hydrochloric acid formed in the third step caused amide hydrolysis or other side reactions with the R group, then an alternative synthesis was used as shown below in Figure 3. The sodium salt of the amine, or amide, was prepared and condensed with the acid chloride to form the respective amide or imide.

To prepare other substituted alkylaminothiazoles, free radical chemistry of the methyl group was invoked as shown below in Figure 4. Utilizing benzoyl peroxide in carbon tetrachloride on **1b** afforded a 24% yield of the desired chloromethyl derivative **1k**. However a more efficient route was discovered, on changing to the reagent sulfuryl chloride. Irradiating the reaction mixure with 366 nm light for 48 hours, a 98% yield of the chloromethyl derivative was obtained.

The idea was to introduce various substituents which could later be readily removed by the insect by reacting the chloromethyl compound with a series of nucleophiles as shown below in Figure 5. For example, reacting thiophenol with triethylamine gave the triethylammonium salt that readily displaced the chloride ion. Potassium cyanide in acetonitrile also worked quite well with

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029


F₃C
O
CF₃
N
N
Cl
S
R
F₃C

1

Figure 1. Structures of the thiazole amide series.

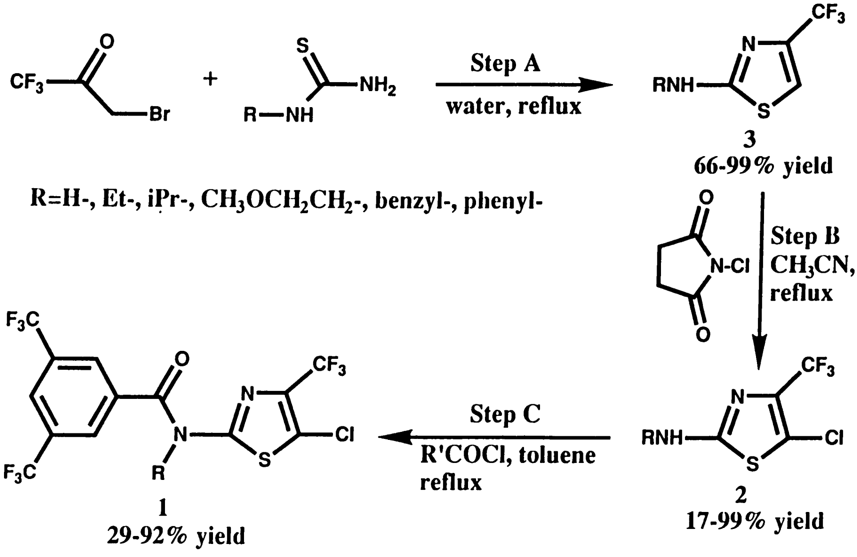

CF₃
O
Br
+
S
NH₂
R—NH
Step A
water, reflux
RNH
N
S
CF₃
3
66-99% yield
R=H-, Et-, iPr-, CH₃OCH₂CH₂-, benzyl-, phenyl-
O
N-Cl
O
Step B
CH₃CN,
reflux
RNH
Cl
2
17-99% yield
Step C
R'COCl, toluene
reflux
F₃C
F₃C
R
1
29-92% yield

Figure 2. Synthesis of thiazole amides.

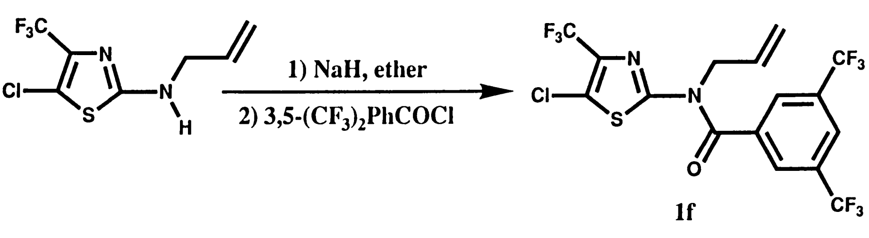

F₃C
Cl
N
S
O
CH₃
N
H
1) NaH, ether
2) 3,5-(CF₃)₂PhCOCl
CF₃
1d
CF₃
1) NaH, ether
2) 3,5-(CF₃)₂PhCOCl
1f

Figure 3. Synthesis of amides via sodium salts.

18-crown-6. Potassium thiocyanide succeeded in acetone while potassium acetate in acetonitrile reacted well in the presence of 18-crown-6. Potassium iodide was successful if the reaction was repeated two times. Each S_N2 transformation required a different solvent or additive.

To prepare the d3-methyl thiazole **1j** the synthesis shown in Figure 6 below was used. The acetamide protecting group allowed selective alkylation at the amide position provided the acetamide methyl group did not contain electron withdrawing groups. No thiazole N-alkylation or amidate formation occurred with acetamides. We selectively hydrolyzed off the acetamide portion with sodium hydroxide in methanol to give the d3 amide which then was treated with an acid chloride as before to give the d3 methyl thiazole **1j**. In the C-13 NMR of **1j** the d3 methyl appeared as a heptet at 34 ppm.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029

Biological Data:

The above target series of amides **1** was tested in our biological assays (*4,6*). A diet incorporation assay was used where the amides were dissolved in acetone and incorporated thoroughly into the diet of the insect and mortality was measured six days after application of the neonatant tobacco budworms. The center of Table I shows the substituent R and the right side shows the range of diet incorporation values. On repeating this assay a year later these values were still representative on our strain of TBW.

The best examples were the lead compound **1a**, N-acetyl, acetoxymethyl, and iodomethyl derivatives which exhibited TBW insecticidal activity. In the starred cases we observed phytotoxicity on one or more crop or weed species. There were, however, two selective cases; the methyl and benzyl derivatives. Methomyl was used as the standard positive control which exhibited an LC_{50} of 2-3 ppm in our assays. Our strain of TBW was resistant to several insecticides including chlordimeform.

On comparing the N-methyl case **1b** with **1a** in a preliminary mammalian toxicity study, as shown below in Figure 7, **1a** exhibited a rat acute oral toxicity of 69 mg/kg whereas **1b** exhibited a value of 501 mg/kg. Thus, **1b** was roughly seven times safer to mammals and nonherbicidal as well.

Cytochrome P-450 N-Methyl Oxidations:

It was postulated that the N-methyl was hydroxylated by insect cytochrome P-450 enzymes and this intermediate would then lose formaldehyde to give the insecticidal compound **1a** (*7,8*). We attempted to synthesize the hydroxymethyl intermediate but it tended to disproportionate to form dimers, trimers, and tetramers. The apparently stable acetoxymethyl analog did, however exhibit insecticidal activity.

In the literature for drugs there are two mechanisms postulated for cytochrome P-450 oxidations (*9*) shown below in Figure 8. The first involves a loss of a hydrogen atom to give a methyl radical which is then hydroxylated.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029

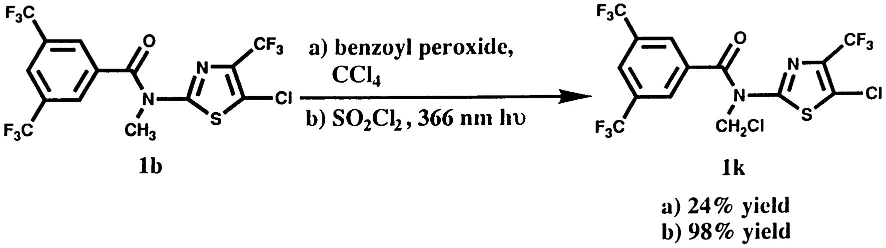

F3C
O
CF3
N
N
Cl
S
F3C
CH3
1b
a) benzoyl peroxide, CCl4
b) SO2Cl2, 366 nm hν
F3C
O
CF3
N
N
Cl
S
F3C
CH2Cl
1k
a) 24% yield
b) 98% yield

Figure 4. Synthesis of N-chloromethyl thiazoles.

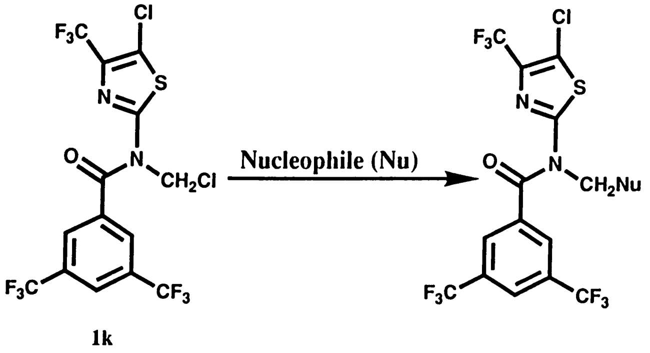

Cl
F3C
S
N
O
N
CH2Cl
F3C
CF3
1k
Nucleophile (Nu)
Cl
F3C
S
N
O
N
CH2Nu
F3C
CF3

Figure 5. Synthesis of N-alkyl substituted thiazoles.

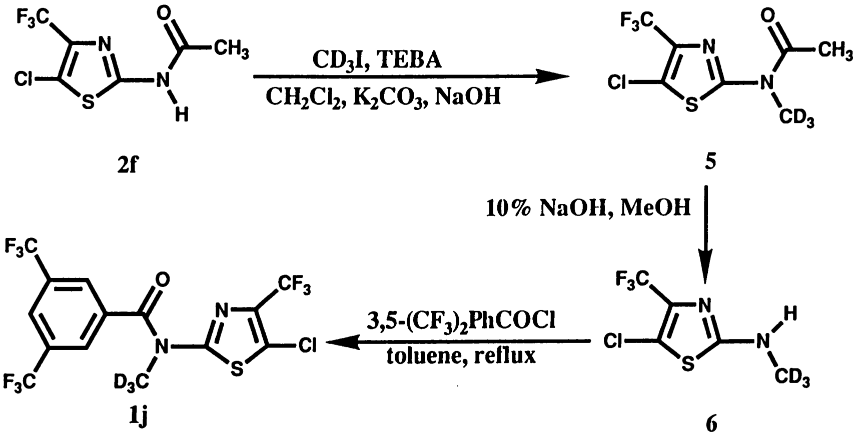
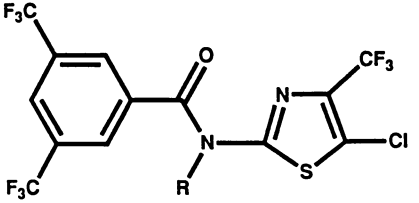
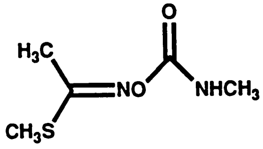

F3C
N
O
CH3
Cl
S
N
H
2f
CD3I, TEBA
CH2Cl2, K2CO3, NaOH
F3C
N
O
CH3
Cl
S
N
CD3
5
10% NaOH, MeOH
F3C
N
H
Cl
S
N
CD3
6
3,5-(CF3)2PhCOCl
toluene, reflux
F3C
O
CF3
N
N
Cl
S
F3C
D3C
1j

Figure 6. Synthesis of d3 amide 1j.

Table I. Biological Data



1

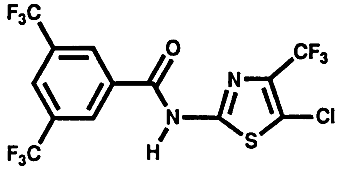


Methomyl

Number	R-	TBW LC-50 diet incorp.
1a	H-	1-10 ppm *(phytotoxic)
1b	Me-	70-125 ppm
1c	Et-	inactive
1d	Allyl-	inactive
1e	iPr-	inactive
1f	Acetyl-	1-10 ppm *
1g	MeOEt-	inactive
1h	Benzyl-	5-10 ppm
1i	Ph-	inactive
1j	d3-Me-	inactive
1k	Cl-Me-	inactive *
1l	PhS-Me-	inactive
1m	NC-Me-	50-100 ppm *
1n	NCS-Me-	10-50 ppm *
1o	AcO-Me-	1-10 ppm *
1p	3,5-CF3Bz-Me-	inactive
1q	I-Me-	1-10 ppm *
Methomyl	-	2-3 ppm

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029

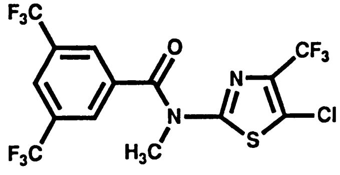

F3C
O
CF3
N
N
Cl
S
H
F3C

1a

Rat acute oral LD_{50} 69mg/kg

Rabbit dermal LD_{50} >200mg/kg

Severe rabbit eye irritation


F3C
O
CF3
N
N
Cl
S
H3C
F3C

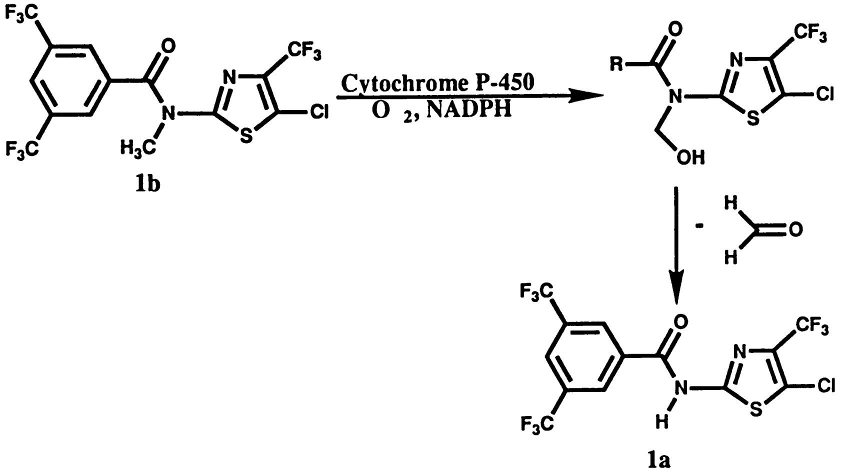
1b

Rat acute oral LD_{50} 501mg/kg

Rabbit dermal LD_{50} >200mg/kg

Slight rabbit eye irritation

Figure 7. Mammalian toxicity of N-thiazoyl amides.


F3C
O
CF3
N
N
Cl
S
H3C
F3C
1b
Cytochrome P-450
O 2, NADPH
R
O
CF3
N
N
Cl
S
OH
-
H
O
H
F3C
O
CF3
N
N
Cl
S
H
F3C
1a

Mechanism A:

$$RR'N{-}CH_3 \xrightarrow[k_H/k_D \sim 8]{\text{-H atom}} RR'N{-}CH_2\cdot \longrightarrow RR'N{-}CH_2OH$$

Mechanism B:

$$RR'N{-}CH_3 \xrightarrow[k_H/k_D \sim 3]{-e^-} RR'\overset{\bullet+}{N}{-}CH_3 \xrightarrow{-H^+} RR'N{-}CH_2\cdot \uparrow$$

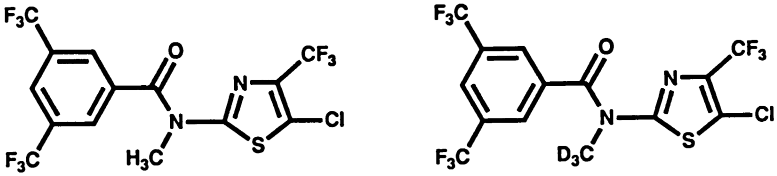
Figure 8. Cytochrome P-450 oxidation.

This mechanism exhibits a very strong kinetic deuterium isotope effect of, on average, about eight and can range from about six to eleven. An example of an enzyme which operates in this range is horseradish peroxidase which has a kH/kD of 8.72. A C-D bond which is stronger than a C-H bond is being broken giving rise to the large deuterium isotope effect.

The second mechanism involves the loss of an electron followed by a loss of a proton to give the same radical. In this case the bond is broken later in the transition state exhibiting a reduced kinetic deuterium isotope effect.

If either mechanism was operative in the insect, we should observe a reduction in insect mortality for the d3 methyl case. A special assay was run comparing side by side **1a** and **1j**. Compound **1b** repeatedly exhibited a LC$_{50}$ of 109 ppm (+/- 20 ppm). **1j** exhibited essentially no activity up to 500 ppm.

These results shown in Figure 9 below suggest that the deuterium isotope effect is operational resulting in a greater than five fold difference in hydroxymethylation, and hence, activation rate. Breaking the methyl C-H bond lies on the pathway to creating an insecticide. This effect is due to the sum of different enzymes which are present in the insect (*10*). We assume that the deuterium atom has a negligible effect on transport within the insect.



1b TBW LC $_{50}$ ~ 90 ppm **1j** TBW LC $_{50}$ >500 ppm

Figure 9. Deuterium isotope effect in TBW mortality.

Conclusion:

The N-methyl and N-benzyl groups are the best substituents of seventeen tested for the amide nitrogen in conferring selective insecticidal activity. N-Alkyl thiazoles with unsubstituted alkyl groups consistently exhibit reduced herbicidal effects. The remarkable difference in TBW insecticidal activity between **1b** and **1j** indicates that **1b** is acting as a proinsecticide. It remains to be shown in situ that **1b** is converted to **1a**. When several metabolites are simultaneously present within the insect it becomes impossible to ascribe the resulting mortality to any one of them. Thus this type of deuterium incorporation experiment will only work if it is operating on the first step in the transformation. Deuterium incorporation studies may be a valuable mechanistic tool for investigation of other whole organism processes. This type of experiment has not been commonly applied in agriculture to date.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029

Acknowledgments:

We thank Steve Sims and Paul Gahr who performed several insect assays as well as Gabriel Srouji and Diane Broccolino who generously provided us several thiazole samples and Peter Beak who contributed expert advice on this project.

Literature Cited:

1. Brooks, G. T. In *Progress in Drug Metabolism*; Bridges, J. W.; Chasseaud, L. F., Eds.; Taylor and Francis: 1984; Vol. 8, 101-188.
2. Fukuto, T. R. In *Pesticide Synthesis Through Rational Approaches*; Magee, P. S.; Kohn, G. K.; Menn, J. J., Eds.; American Chemical Society: Washington, D. C., 1984; Vol. 255; 87-101.
3. Drabek, J.; Neuman, R. In *Progress in Pesticide Biochemistry and Toxicology*; Hutson, D. H.; Roberts, T. R.;,Eds.; Wiley and Sons: New York, New York, 1985, Vol. 5; 35-87.
4. Wilkes, M. C.; Lavrik, P. B.; Greenplate, J. *J. Agric. Food Chem.* **1991**, *39*, 1652-1657.
5. Kaye, P. T.; Meakins, G. D.; Willbe, C.; Williams, P. R. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2335-2339.
6. Marrone, P. G.; Ferri, F. D.; Mosley, T. R.; Memke, L. J. *J. Econ. Entomol.*, **1985**, *78*, 290-293.
7. Metcalf, R. L.; Fukuto, T. R.; Collins, C.; Borck, K.; El-Aziz, S. A.; Munoz, R.; Cassil, C. C. *J. Agric. Food Chem.*, **1968**, *16*, 300-311.
8. Guengerich, F. P.; Macdonald, T. L. *Acc. Chem Res.* **1984**, *17*, 9-16.
9. Miwa, G. T.; Walsh, J. S.; Kedderis, G. L.; Hollenberg, P. F. *J. Biol.*, **1983**, *258*, 14445-14449.
10. Levine, W. G. *Drug Metabolism Reviews*, **1991**, *23*, 253-309.

RECEIVED February 10, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch029

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch030

Chapter 30

Diphenylamines I

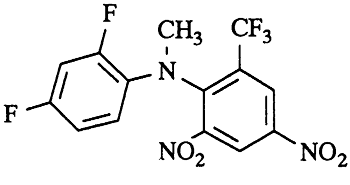
Synthesis and Structure–Activity Relationship Development of Novel *N*-(Substituted-phenyl)-*N*-alkyl-2-(trifluoromethyl)-4,6-dinitrobenzenamines Leading to a Potent Miticide (El-462)

B. A. Dreikorn[1], K. E. Kramer[1], D. F. Berard[1], R. W. Harper[2], E. Tao[2], L. G. Thompson[1], and J. A. Mollet[1]

[1]DowElanco Research Laboratories, P.O. Box 708, Greenfield, IN 46140
[2]Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285

A series of N-alkyl-2-(trifluoromethyl)-4,6-dinitrodiphenylamines was prepared for evaluation as agricultural miticides. This work led to the discovery and development of EL-462, a miticide highly active against two-spotted spider mites (*Tetranychus urticae*). The synthesis, structure-activity-relationship, and efficacy of these diphenylamines will be discussed.

For a number of years, the agricultural component of Lilly Research Laboratories, now a part of DowElanco, has been interested in diphenylamines because of their fungicidal(*1-3*) and rodenticidal activity(*4-7*). In the course of this work EL-462, N-methyl-2,4-difluoro-2',4'-dinitro-6'-(trifluoromethyl)- diphenylamine, was prepared and broadly screened. Although it possessed little or no fungicidal activity, it was found to control two-spotted spider mites in our screen at levels below 10 ppm and yet exhibited relatively low acute mammalian toxicity and low phytotoxicity. Although similar diphenylamines are known to be miticidal(*8-9*), this activity is usually accompanied by mammilian toxicity and phytotoxicity. Based on this lead, an SAR approach was developed.



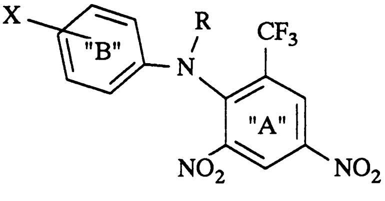
EL - 462

0097–6156/92/0504–0336$06.00/0

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch030

STRUCTURE-ACTIVITY-RELATIONSHIP APPROACH

The SAR approach that we followed was to hold ring "A" constant (since, in our screens, only diphenlamines with this substitution pattern in ring A were miticidally active), and substitute both ring "B" and the nitrogen between the rings.

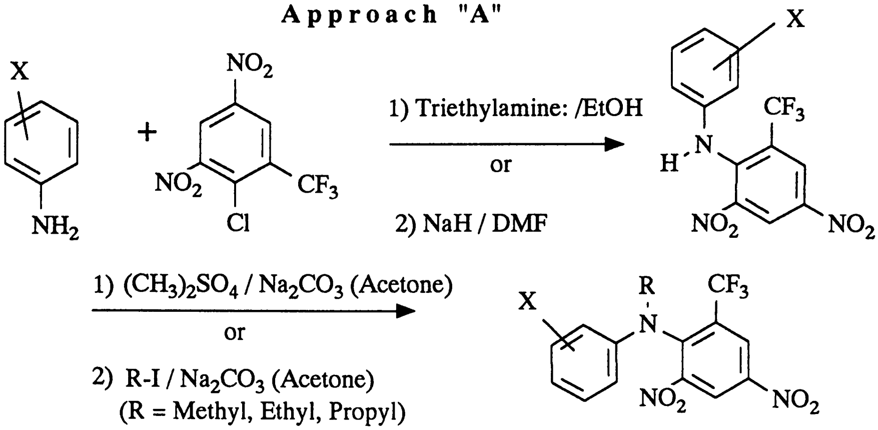

X
"B"
R
N
CF3
"A"
NO2
NO2

SYNTHESIS OF ANALOGS

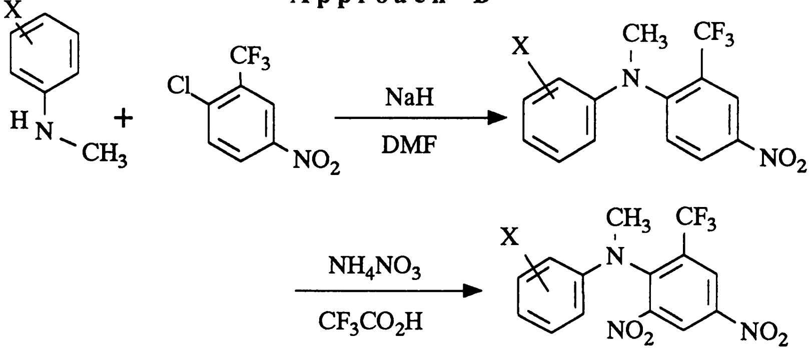
Three approaches were used in synthesizing all of the analogs of EL-462 outlined in the SAR(*10*) (see Synthetic Schemes below); (A) the formation of the diphenylamine followed by the N-alkylation, (B) the N-alkylation of the aniline followed by the formation of the diphenyl amine,and (C) substitution of the phenyl group after formation of the N-alkylated diphenylamine.

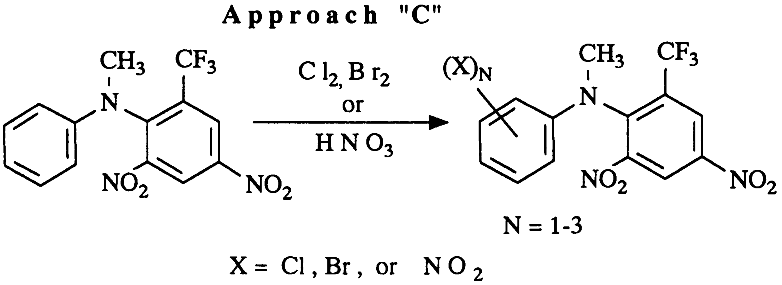
SYNTHETIC SCHEMES

Approach "A"


X
NH2
+
NO2
NO2
CF3
Cl
1) Triethylamine: /EtOH
or
2) NaH / DMF
X
H
N
CF3
NO2
NO2
1) (CH3)2SO4 / Na2CO3 (Acetone)
or
2) R-I / Na2CO3 (Acetone)
(R = Methyl, Ethyl, Propyl)
X
R
N
CF3
NO2
NO2

Approach "B"


X
H
N
CH3
+
CF3
Cl
NO2
NaH
DMF
X
CH3
CF3
N
NO2
NH4NO3
CF3CO2H
X
CH3
CF3
N
NO2
NO2



Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch030

SCREENING METHODS:

Initial screening against two-spotted spider mite was performed on Kentucky Wonder beans in the greenhouse. Ten-day old plants were placed in contact with mite-infested leaves for two days and then three rates of a formulated solution of each compound was sprayed to runoff on the infected leaves, with four replicates. After two days an actual count of the mites surviving on 6.28 cm^2 of leaf surface was made and the concentration that controlled 50% of mites (LC_{50}) was determined (Table I).

SAR TRENDS

The best miticidal activity was observed in those compounds where the phenyl ring "B" is either mono- or poly-substituted with halogens, especially chlorine and fluorine. With the exception of the CF_3 substituted compounds, those substituted in the phenyl ring with other electron-withdrawing groups were for the most part less active than the halogen compounds. In the case of electron-withdrawing groups, the "3" substitution gives the best activity while, in the case of halogens, the "4" position must be substituted for maximum activity. After the completion of the SAR, the best candidate for potential commercialization, based on efficacy, cost and degree of mammalian toxicity was EL-462, our lead compound. After completion of the screening SAR, the most active compounds were further compared from the standpoints of miticidal efficacy, phytotoxicity and acute LD_{50} in mice. As a result of these studies, the best candidate for potential commercialization, based on efficacy, cost and the degree of mammalian toxicity and phytotoxicity was EL-462, our lead compound. In addition to the mite activity seen with EL-462, a wide spectrum of insect pests in our screens were also controlled but required higher rates.

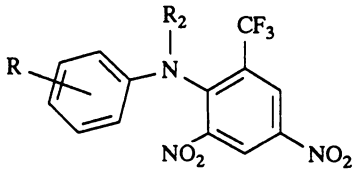
COMPARATIVE PHYTOTOXICITY OF THE N-H COMPOUNDS WITH N-ALKYL ANALOGS

In our screens, the diphenylamines without the N-alkyl groups, although miticidal, tended to be very phytotoxic. We postulated that this phytotoxicity was associated with the acidic proton on the amine "tether". To determine how general this phenomenon was we compared the relative phytotoxicity of a number of miticidally active diphenylamines, both with and without alkyl groups on the amine "tether". This was accomplished by spraying ten-day-old soybean plants with varying rates of formulated material, up to 4000 ppm, and, after 7 days the plants were examined for signs of chlorosis or burning (Table II). Without exception, the N-alkylated diphenylamines were from 16 to 500 times less phytotoxic than their N-H counterparts.

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch030

TABLE I

ACTIVITY OF DIPHENYLAMINES AGAINST TWO-SPOTTED SPIDER MITES

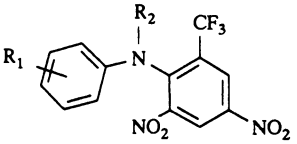


R_1	R_2	LC_{50} RANGE (PPM)
H	Methyl	> 1000
2-Fluoro	Methyl	> 1000
3-Fluoro	Methyl	> 100 < 1000
4-Fluoro	Methyl	> 10 < 50
2-Chloro	Methyl	> 1000
3-Chloro	Methyl	> 10 < 50
4-Chloro	Methyl	> 10 < 50
3-Bromo	Methyl	> 100 < 1000
4-Bromo	Methyl	> 10 < 50
4-Bromo	Ethyl	> 10 < 50
4-Iodo	Methyl	> 10 < 50
2-CF_3	Methyl	> 100 < 1000
3-CF_3	Methyl	> 1 < 10
3-CF_3	Ethyl	> 1000
4-CF_3	Methyl	> 10 < 50
2-Cyano	Methyl	> 1000
3-Cyano	Methyl	> 100 < 1000
4-Cyano	Methyl	> 1000
4-Cyano	Ethyl	> 10 < 50
3-Nitro	Methyl	> 100 < 1000
4-Nitro	Methyl	> 1000
3-Methyl	Methyl	> 1000
2,4-Difluoro	Methyl	> 10 < 50
2,4-Difluoro	Ethyl	> 10 < 50
2,5-Difluoro	Methyl	> 1000
3,4-Difluoro	Methyl	> 1 < 10
2,6-Difluoro	Methyl	> 100 < 1000
2,4-Dichloro	Methyl	> 10 < 50
3,4-Dichloro	Methyl	> 10 < 50
3,5-Dichloro	Methyl	> 50 < 100
2,4-Dibromo	Methyl	> 10 < 50
3,4-Dibromo	Methyl	> 100 < 1000
2,4-Dinitro	Methyl	> 1000
2-Chloro-5-CF_3	Methyl	> 50 < 100
2-Methyl-4-Chloro	Methyl	> 1000
2,4,6-Trifluoro	Methyl	> 1 < 10
2,4,6-Trichloro	Methyl	> 10 < 50
2,4,6-Trichloro	Ethyl	> 10 < 50
2,4,6-Trichloro	Propyl	> 10 < 50
2,4-Difluoro-6-Nitro	Methyl	> 50 < 100
2,4,6-Tribromo	Methyl	> 1000
2,3,5,6-Tetrafluoro	Methyl	> 100 < 1000
2,3,4,5,6-Pentafluoro	Methyl	> 100 < 1000

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch030

TABLE II

COMPARATIVE PHYTOTOXICITY OF N-H vs N-ALKYL DIPHENYLAMINES ON SOYBEANS



R_1	R_2	HIGHEST RATE (PPM) WITHOUT PHYTOTOXICITY
2-Fluoro	H	62
	CH_3	> 4000
3-Fluoro	H	31
	CH_3	500
4-Fluoro	H	31
	CH_3	2000
2-Chloro	H	< 31
	CH_3	> 4000
3-Chloro	H	< 31
	CH_3	> 4000
4-Chloro	H	< 31
	CH_3	> 4000
3-Bromo	H	< 31
	CH_3	> 4000
4-Bromo	H	< 31
	CH_3	> 4000
4-Iodo	H	< 31
	CH_3	> 4000
3-CF_3	H	8
	CH_3	> 4000
4-CF_3	H	< 8
	CH_3	1000
2,4-Difluoro	H	16
	CH_3	> 4000
2,4-Difluoro	H	< 31
	CH_2CH_3	> 4000
2,5-Difluoro	H	< 31
	CH_3	2000
2,6-Difluoro	H	< 31
	CH_3	> 4000
3,4-Difluoro	H	< 31
	CH_3	1000
3,5-Dichloro	H	< 31
	CH_3	> 4000
2,4-Dibromo	H	< 31
	CH_3	> 4000
2,4,6-Trifluoro	H	< 31
	CH_3	> 4000
2,4,6-Trichloro	H	< 31
	CH_3	1000
2,4,6-Trichloro	H	< 31
	CH_2CH_3	1000
2,4,6-Trichloro	H	< 31
	$CH_2CH_2CH_3$	1000
2,3,5,6-Tetrafluoro	H	< 31
	CH_3	> 4000
Pentafluoro	H	< 31
	CH_3	> 4000
Pentachloro	H	62
	CH_3	> 4000

FIELD ACTIVITY

EL-462 was field-tested against two-spotted spider mite infestations of soybeans, cotton, mung beans, eggplant, marigolds, almond trees, and peach trees. The compound was typically applied as an emulsifiable concentrate or wettable powder at rates between 0.25 and 2 lb/acre at 1-2-week intervals. Over 90% control was observed at rates of 0.5-1 lb/acre with no phytotoxicity. It was also tested against citrus red mite (*Panonychus citri*) and citrus rust mite (*Phyllocoptruta oleivora*) infestations of orange trees. In the case of the citrus red mite, between 60-80% control was obtained depending on the rates used (1 to 4 lb/acre). In the case of citrus rust mite, 81% control was observed at 2.0 lb/acre. We also tested EL-462 against European red mite (*Panonychus ulmi*) on apples. Between 85-90% control was obtained at rates between 1 to 2 lb/acre. In addition to the mite activity seen with EL-462, a wide spectrum of insect pests were also controlled but at higher rates.

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch030

CONCLUSION

From the initial observation that EL-462 controlled two-spotted spider mites in the greenhouse, we were able to carry out an SAR to further define the structural requirements for both miticidal activity and low phytotoxicity. The SAR led to the conclusions that the N-alkyl group on the diphenylamine was essential to reduce phytotoxicity and also that of all the compounds screened, EL-462 had the greatest promise for commercialization since it is both highly active against mites while exhibiting very low phytotoxicity. Field studies confirmed that EL-462 indeed possessed good miticidal activity and low phytotoxicity, however the rates that were required for activity proved to be unacceptable for further development because of cost and potential residue considerations.

ACKNOWLEDGMENTS

We would especially like to thank Dr. James Froyd, formerly of Lilly Research Laboratories, for conducting all the comparative phytotoxicity tests and Dr. Pierre Daniau of our European affiliate for his contributions.

LITERATURE CITED

1. Dreikorn, B.A., U.S. Patent 4,152,460, **1979**.
2. Dreikorn, B.A.; Kramer, K.E., U.S. Patent 4,381,312, **1983**.
3. Dreikorn, B.A., U.S. Patent 4,187,318, **1980**.
4. Dreikorn, B.A., U.S. Patent 4,084,004, **1978**.
5. Dreikorn, B.A., U.S. Patent 4,140,778, **1979**.
6. Dreikorn, B.A., O'Doherty, G.O.P.; Clinton, A.J.; Kramer, K.E. *Proceedings 1979 British Crop Protection Conference*. **1979**, pp. 491-498
7. Dreikorn, B.A.; O'Doherty, G.O.P.; A.C.S. Symposium series 255, *Pesticide Synthesis Through Rational Approaches*, Chapter 4, **1984**.
8. Barlow, C.B. *et.al.*, U.S. Patent 4,117,167, **1978**
9. Grantham, G.D., U.S. Patents 4,215,145, **1980** and 4,341,772, **1982**
10. Dreikorn, B.A.; Kramer, K.E., U.S. Patent 4,407,820, **1983**

RECEIVED June 16, 1992

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch031

Chapter 31

Diphenylamines II

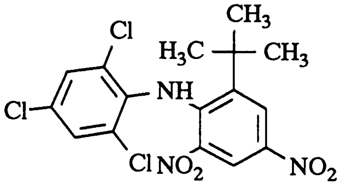
Synthesis and Miticidal Activity of 2-Alkyl-4,6-dinitro- and 4-Alkyl-2,6-dinitrodiphenylamine Analogs and Derivatives

K. E. Kramer, B. A. Dreikorn, W. H. Humphreys, and J. A. Mollet

DowElanco Research Laboratories, P.O. Box 708, Greenfield, IN 46140

Polynitrodiphenylamines have exhibited interesting biological activity in many agrochemical areas. Two classes, N-(substituted phenyl)-2-alkyl-4, 6- dinitrobenzenamines and N-(substituted phenyl)-4-alkyl-2,6-dinitro benzenamines, have demonstrated excellent activity against mites, especially citrus rust mite, *Phyllocoptruta oleivora*. The synthesis and structure-activity-relationships of these diphenylamines will be described.

For a number of years, the agricultural component of Lilly Research Laboratories, now a part of DowElanco, has been interested in diphenylamines because of their fungicidal(*1-3*) and rodenticidal(*4-7*) activity. In the course of this work Compound 1, 2,4,6-trichloro-2'-t-butyl-4',6'dinitrodiphenylamine, was prepared and broadly screened. Although it possessed little or no fungicidal or rodenticidal activity, it was found to control two-spotted spider mite (*Tetranychus urticae*), Mexican bean beetle (*Epilachna varivestis*) and southern army worm (*Spodoptera eridanie*) in our screen at levels below 10 ppm and yet exhibited relatively low acute mammalian toxicity and low phytotoxicity. Although the level of insecticidal control was not sufficient for further development, the miticidal activity was of great interest, especially when Compound 1 was observed to control citrus rust mites on orange trees. This activity and the fact that these were unique compounds with relatively low mammalian toxicity encouraged us to initiate a structure-activity-relationship.



Compound 1

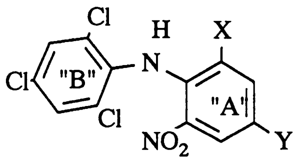
0097–6156/92/0504–0342$06.00/0

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

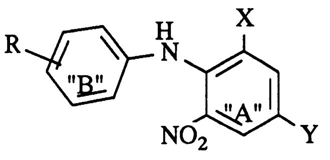
Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch031

STRUCTURE-ACTIVITY-RELATIONSHIP APPROACH

A two-pronged approach to the SAR was followed. First, the "B" ring, the 2,4,6-trichlorophenyl, was held constant and alkyl groups were placed in the ortho (X) or para (Y) positions of the "A" ring, with a nitro groups occupying the other position (Structure I). After it was determined that the t-butyl group was the best alkyl group for miticidal activity (Table I), the second approach was to hold the "A" ring constant with the t-butyl in the ortho (X) or para (Y) position and substitute the "B" ring with a variety of electron donating or withdrawing atoms or groups (Structure II). The results of this study can be seen in Table II.



Structure I



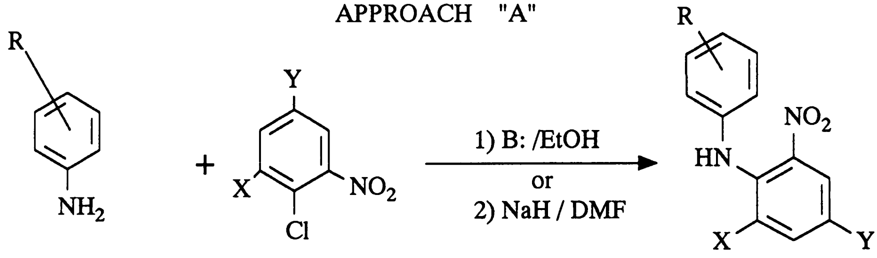
Structure II

SYNTHESIS OF ANALOGS

Two approaches were used in synthesizing all of the analogs of structures I and II(*8*); (A) the formation of the diphenylamine from substituted anilines and the appropriately substituted dinitrochlorobenzenes and (B) substitution of the phenyl group after formation of the diphenylamine. The alkyl-dinitrochlorobenzenes used in these approaches were synthesized from nitration and subsequent chlorination of the corresponding alkyl phenols (see Synthetic Scheme).

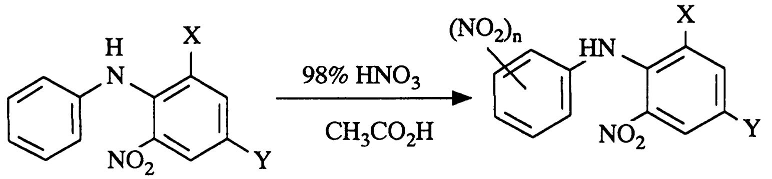
SYNTHETIC SCHEME

APPROACH "A"



R = Various substitutuents

APPROACH "B"



X = Nitro or Alkyl

Y = Alkyl or Nitro

n = 1 or 2

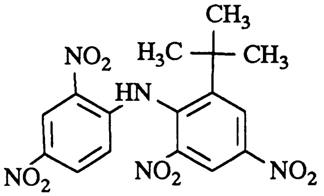
Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch031

SCREENING METHODS

All of the screening against citrus rust mites was conducted on live orange trees in the field. Infected leaves were marked and then sprayed to runoff with formulated suspensions of each test compound at two rates (1000 and 100 ppm). At various intervals after treatment, counts of remaining live mites were taken and the percent control noted. Because the primary screening for citrus rust mite control had to be conducted in the field, greater variations in control were observed. (For example, in Table I, the "para" n-pentyl compound appears to be the equal of the "ortho" and "para" t-butyl compounds. However, we believe this to be one of many artifacts caused by weather conditions in the field. When run at other rates the para n-pentyl compound failed to demonstrate the level of activity shown in Table I). The compound data is recorded on Tables I and II. The compounds that showed exceptional activity at 100 ppm (indicated by * on Table II) underwent additional efficacy evaluation.

SAR TRENDS

The best miticidal activity was observed in those compounds where the alkyl group on ring "A" is t-butyl and where the phenyl ring "B" is either mono- or poly-substituted with halogen atoms or nitro groups. When additional special testing was carried out, Compound **2**, the 2,4-dinitro analog, appeared to give the best overall miticidal activity and was chosen for further development.



Compound **2**

FIELD ACTIVITY

Compound **2** was field tested against both two-spotted spider mite and citrus rust mite. Although it demonstrated good control of the two-spotted spider mite at rates of 1000 ppm, it gave excellent control of citrus rust mite at lower rates. In numerous whole-branch trials on both orange and grapefruit trees in Florida and Texas, Compound **2** was found to be efficacious at rates of 100 ppm for periods of up to eight weeks.

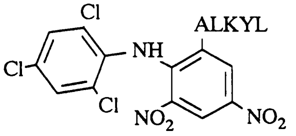
CONCLUSION

From the observation that Compound 1 controlled two-spotted spider mites in the greenhouse and citrus rust mites in the field, we were able to carry out an SAR to further define the structural requirements for both miticidal activity and phytotoxicity. The SAR led to the conclusion that Compound **2** had the greatest promise for commercialization from among a number of active analogs due to its high activity against citrus rust mites and relatively low toxicity in both mammals and plants. Field studies confirmed that Compound **2** indeed possessed good miticidal activity and low phytotoxicity but only at rates that prohibited the commercialization because of cost and residue considerations.

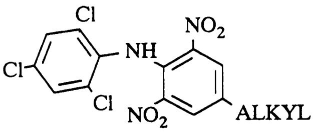
Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch031

TABLE I

RESULTS OF SCREENING DIFFERENT ALKYL GROUPS IN THE RING SYSTEMS "A" AND "B" AGAINST CITRUS RUST MITE



"A"



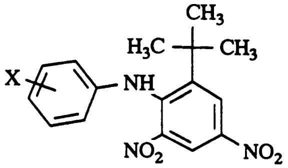
"B"

ALKYL STRUCTURE	TYPE	RATE	PERCENT CONTROL OF CITRUS RUST MITES
Methyl	A	1000	19
		100	31
	B	1000	0
		100	0
Ethyl	A	1000	32
		100	--
	B	1000	0
		100	78
n-Propyl	A	1000	82
		100	0
	B	1000	93
		100	69
i-Propyl	A	1000	93
		100	81
	B	1000	74
		100	0
n-Butyl	B	1000	70
		100	--
Methylpropyl	A	1000	84
		100	21
i-Butyl	B	1000	0
		100	13
t-Butyl	A	1000	87
		100	89
	B	1000	90
		100	89
1-Methylbutyl	A	1000	84
		100	0
n-Pentyl	B	1000	95
		100	89
1,1-Dimethyl propyl	B	1000	85
		100	50
n-Hexyl	B	1000	62
		100	--
Cyclohexyl	A	1000	100
		100	13
	B	1000	100
		100	13

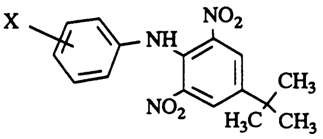
Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch031

TABLE II

RESULTS OF SCREENING t-BUTYL DIPHENYLAMINES AGAINST CITRUS RUST MITE



"A"



"B"

SUBSTITUTION (X)	TYPE	RATE	PER CENT CONTROL 10-14 DAYS
H	A	1000	45
		100	44
	B*	1000	84
		100	89
4-Fluoro	A	1000	97
		100	57
	B*	1000	83
		100	80
2-Chloro	B	1000	84
		100	95
3-Chloro	B	1000	40
		100	63
4-Chloro	A	1000	70
		100	62
	B	1000	34
		100	53
2-Bromo	A	1000	73
		100	42
3-Bromo	A	1000	77
		100	48
	B	1000	74
		100	0
4-Bromo	A	1000	65
		100	61
	B*	1000	95
		100	89
4-Iodo	A	1000	81
		100	75
	B	1000	51
		100	0
4-Cyano	A*	1000	72
		100	96
	B	1000	87
		100	0
4-Methyl	B	1000	88
		100	60
4-t-Butyl	A	1000	69
		100	0
4-Acetyl	A	1000	34
		100	2
4-Carbethoxy	A	1000	54
		100	69
4-Nitro	A	1000	86
		100	18
	B	1000	80
		100	21

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch031

TABLE II *CONTINUED*

SUBSTITUTION (X)	TYPE	RATE	PER CENT CONTROL 10-14 DAYS
2-Nitro	A	1000	--
		100	64
	B	1000	81
		100	0
4-CF_3	A*	1000	96
		100	94
	B	1000	0
		100	0
3-CF_3	A*	1000	96
		100	74
	B	1000	0
		100	46
2-CF_3	A	1000	96
		100	34
4-Benzoyl	A	1000	0
		100	42
2,4-Difluoro	A*	1000	86
		100	78
	B	1000	0
		100	0
2,5-Difluoro	A	1000	67
		100	33
2,4-Dichloro	A*	1000	89
		100	86
	B	1000	96
		100	64
2,3-Dichloro	A	1000	66
		100	14
3,4-Dichloro	A*	1000	88
		100	98
	B	1000	27
		100	46
2,6-Dibromo	A	1000	93
		100	34
2,4-Dimethyl	A	1000	--
		100	20
2,4-Dinitro	A*	1000	97
		100	94
	B	1000	94
		100	53
3,5-Di-CF_3	A	1000	98
		100	56
2,4,6-Trifluoro	A*	1000	54
		100	86
2,4,6-Trichloro	A*	1000	87
		100	89
	B	1000	90
		100	89
2,4,6-Tribromo	A*	1000	87
		100	98
	B*	1000	90
		100	89
Pentachloro	A	1000	95
		100	56

* COMPOUNDS CHOSEN FOR FURTHER EVALUATION

American Chemical Society
Library
1155 16th St., N.W.
Washington, D.C. 20036

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

ACKNOWLEDGMENTS

We would especially like to acknowledge Dr. Pierre Daniau of our European affiliate for drawing our attention to the miticidal activity of these compounds.

LITERATURE CITED

1. Dreikorn, B.A., U.S. Patent 4,152,460, **1979**.
2. Dreikorn, B.A.; Kramer, K.E., U.S. Patent 4,381,312, **1983**.
3. Dreikorn, B.A., U.S. Patent 4,187,318, **1980**.
4. Dreikorn, B.A., U.S. Patent 4,084,004, **1978**.
5. Dreikorn, B.A., U.S. Patent 4,140,778, **1979**.
6. Dreikorn, B.A.; O'Doherty, G.O.P.; Clinton, A.J.; Kramer K.E. *Proceedings of 1979 Crop Protection Conference.* **1979**, pp 491-498.
7. Dreikorn, B.A.; O'Doherty, G.O.P.; A.C.S. Symposium Series 255, *Pesticide Synthesis Through Rational Approaches*, Chapter 4, **1984**.
8. Dreikorn B.A.; Kramer, K.E., U.S. Patent 4,670,596, **1987**.

RECEIVED March 30, 1992

Downloaded by UNIV OF GUELPH LIBRARY on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch031

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

Chapter 32

Synthesis and Reactivity of Cyclic Hydroxamic Acids

Resistance Factors in the Gramineae

Jeffrey Atkinson[1,3], John Arnason[1], Francisca Campos[1,4], Hermann M. Niemeyer[2], and Héctor R. Bravo[2]

[1]Department of Biology, University of Ottawa, Ottawa K1N 6N5, Canada
[2]Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile

General synthetic methods have been developed which make available a variety of analogues of the maize derived cyclic hydroxamic acid 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA). Analogues include the following structural changes: aryl ring substitution, removal of the phenolic oxygen (to form a tetrahydroquinoline analogue), and removal of the lactol and the hydroxamic hydroxyl groups. Analogues with substituents *para-* to the hydroxamic acid nitrogen have been used to produce linear free energy relationships (LFERs) for the hydroxamic and phenolic pK$_a$s, and for the unimolecular decomposition of these compounds to benzoxazolinones. Reactivity with mercaptoethanol as a model biological nucleophile was also examined. Feeding trials with larvae of *Ostrinia nubilalis* (Hübner) show that biological activity is not adequately described by the *in vitro* reduction by thiols. The demonstrated inhibition of larval gut proteases by DIMBOA is also discussed.

Over thirty years ago the first reports were published on suspected insect resistance factors in maize (*1-5*)and rye (*6*). This early work focused attention on the benzoxazolinones such as 6-MBOA (Figure 1). When it was shown that these were the degradation products of cyclic hydroxamic acid glucosides, (*6,7*) the latter were then suspected to be the true resistance factors. The levels of hydroxamic acids in some cereal grains have been correlated with resistance to some important pests such as the European corn borer, *Ostrinia nubilalis* (Hübner); the western corn rootworm *Diabrotica virgifera virgifera* (LeConte) (*8*); the corn leaf aphid *Rhopalosiphum maidis*; the bird cherry oat aphid *Rhopalosiphum padi* (L.) (*9,10*); the fungi *Helminthosporium turcicum* and *Erwinia* species of bacteria. A thorough discussion of these correlations is included in a recent review on the biology and chemistry of these cyclic hydroxamic acids(*11*). The precise mechanism of action of these allelochemicals, however, has not been completely elucidated. Knowledge of

---

[3]**Current address: National Research Council, Canada, Steacie Institute for Molecular Science, Ottawa, Ontario K1A 0R6, Canada**

[4]**Current address: Merck Sharpe and Dohme, Insecticide Development Laboratories, P.O. Box 2000, Rahway, NJ 07065**

0097–6156/92/0504–0349$06.00/0

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

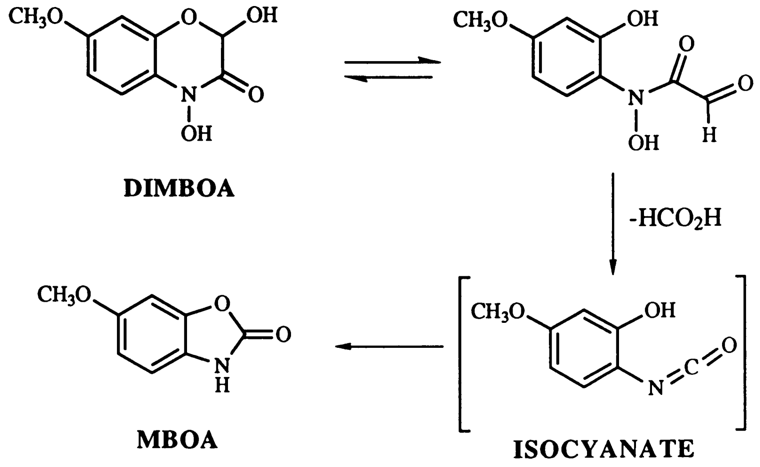


Figure 1. Decomposition of DIMBOA to 7-methoxy-benzoxazolinone, MBOA. From J. Org. Chem. **1991**, *56(5)*, 1788. Copyright 1991 American Chemical Society.

their chemistry is required to interpret accurately feeding trials with insect larvae, and ultimately to support a case for maintaining high levels in cultivated crop varieties. Recent work at the University of Ottawa, (Canada) and the Universidad de Chile, (Santiago, Chile) has delineated several key aspects of the chemistry and biology of this class of compounds. The synthesis of adequate quantities of the naturally occurring materials, as well as various analogues, has enabled detailed investigations of solution stability, reactions with nucleophiles, reduction by thiols, feeding and behavioural trials. This chapter will summarize these results.

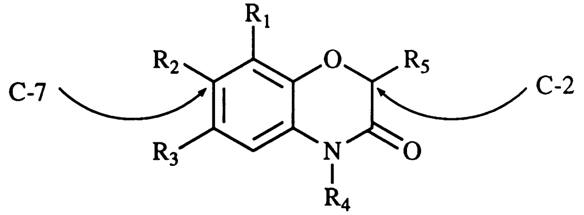
Syntheses

Reductive Cyclizations Honkanen and Virtanen (*12*) reported the first synthesis in this class (DIBOA, Table I) starting from protected nitrophenols, but the yield for a simple four step synthesis was only 3.5 %. The synthesis is problematic since it demanded the use of the carcinogenic chloromethyl methyl ether (MOM-Cl) to protect the phenol and it required that an intermediate arylhydroxylamine be isolated from the zinc/ammonium chloride reduction of the nitro-precursor. This sort of reduction procedes poorly with electron donating substituents such as methoxy on the aryl ring and thus does not allow an efficient synthesis of DIMBOA. The hydroxamates are also recovered as their zinc chelates which must be hydrolysed in strongly acidic media which may limit the choice of substituents.

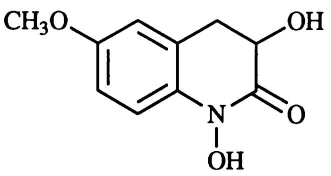
In 1975 a patent was issued to Hoffman-La Roche (*13*) for the synthesis of DIMBOA and a small number of analogues. The construction of the benzoxazinone ring was accomplished by reductive cyclization of suitably functionalized nitroesters either with zinc/ammonium chloride or a method first developed by Coutts (*14*) using palladium on charcoal and sodium borohydride in aqueous dioxane (Figure 2). The latter method is quite general. (The catalyst should be handled as a suspension in water since any loose particles that adhere to the reaction flask can ignite the hydrogen that is

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

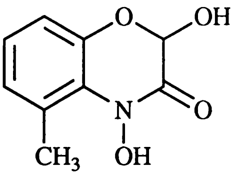
Table I. Cyclic hydroxamic acids and lactams available by synthesis



Compound	R_1	R_2	R_3	R_4	R_5	Acronym
1	H	MeO	H	OH	OH	DIMBOA
2	H	MeO	H	H	OH	HMBOA
3	H	$-OCH_2O-$		OH	OH	
4	H	MeO	MeO	OH	OH	
5	MeO	MeO	H	OH	OH	DIM_2BOA
6	H	*t*-Bu	H	OH	OH	
7	H	Me	H	OH	OH	
8	H	Me	H	OH	H	
9	H	H	H	OH	OH	DIBOA
10	H	Cl	H	OH	OH	
11	H	Cl	H	OH	H	
12	H	F	H	OH	OH	
13	H	F	H	OH	H	
14	H	CO_2Me	H	OH	OH	
15	H	CO_2Me	H	OH	H	
16	H	NO_2	H	OH	OH	
17	H	CF_3	H	OH	MeO	
18	H	CN	H	OH	OH	
19	H	CN	H	OH	H	
20	H	MeO	H	OH	MeO	
21	H	MeO	H	OH	H	
22	H	H	H	OH	H	
23	H	H	H	H	OH	



24



25

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

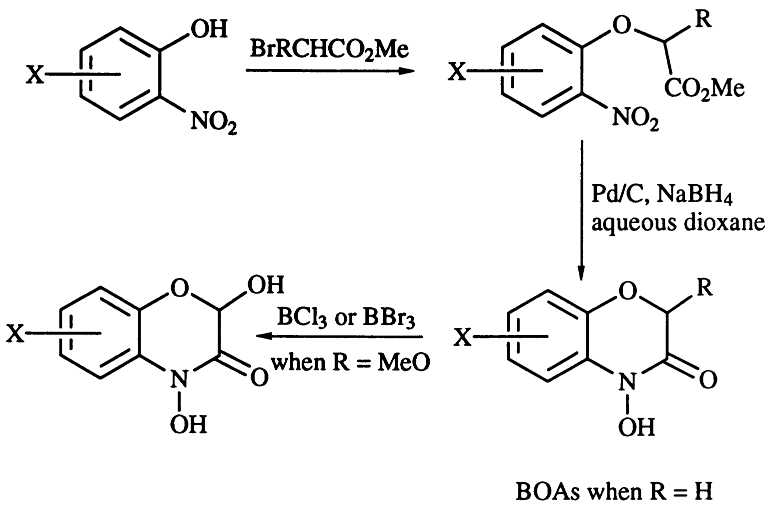


Figure 2. Synthesis of cyclic hydroxamic acids by reductive cyclization. From J. Org. Chem. **1991,** *56(5),* 1788. Copyright 1991 American Chemical Society.

evolved from the mixture.) Once cyclized the lactol at C-2 is unmasked by demethylation with boron trichloride or tribromide in methylene chloride. We have synthesized several new analogues (*15*) (Table I) most of which had varied substituents para to the hydroxamic acid nitrogen (R_2) since this would most directly affect the electronic nature of the nitrogen. In Table I, compounds **1, 9** and **20** have been described in the literature (*13*) as have **2, 21-23** (*16,17*). A series of 7-substituted 4-hydroxy-1,4-benzoxazin-3-ones (R_5=H in Table I) have also been synthesized by this method (*15,18*). The only substrates that could not be successfully cyclized to the hydroxamic acid had strong electron donating groups on the aryl ring. When R_2 was dimethylamino or acetamido (and R_5=MeO) the reactions were highly coloured and only amides, products of over reduction, were isolated. This is a common problem with attempts at partial reduction of electron rich nitroaromatics. Even the rather selective technique of transfer hydrogenation (*19*) is most efficiently performed on unsubstituted or halogenated nitroaromatics when hydroxylamine products are desired.

Compound **24** has had the phenolic oxygen replaced by a methylene group which removed the lactol moiety in a different manner to those analogues where R_5=H. It was readily synthesized (*15*) by acylation of the benzyl anion (potassium tert-butoxide) of 5-methoxy-2-nitrotoluene with diethyloxalate, followed by an identical reductive cyclization as mentioned above, which concomitantly reduces the carbonyl of the initial α-ketoester.

Demethylation With Boron Trihalides The demethylation of the acetals was generally very efficient with yields usually in the 60 -90% range. The boron trihalides can be purchased commercially as solutions in methylene chloride and can be safely handled by common syringe techniques for moisture sensitive materials. In the case of compounds **3, 4** and **5** control of temperature and reaction time were essential since the aryl methoxy and methylenedioxy groups are also easily cleaved by these reagents. Yields in these cases were 20-40% after purification on Fe^{3+}-Sephadex (20). As R_2

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

becomes increasingly electron withdrawing the ease of demethylation decreases to the point where with the cyano and trifluoromethyl analogues no reaction occurred, even with the more reactive boron tribromide. For compound **14** it is best to work with the ethyl ester since this functionality reacts very slowly with these reagents, unlike the methyl esters. It should be noted that these acetals are not amenable to preparative hydrolysis with aqueous acids. Prolonged exposure to a variety of acids (hydrochloric, hydrobromic, sulfuric, perchloric, acetic, trifluoroacetic) produced a number of coloured products in minor amounts, but the bulk of the acetal remained unchanged.

Lactol Formation Via Bromination The C-2 lactol has also been elaborated by bromination and hydrolysis after reductive ring closure to form the benzoxazinone hydroxamic acid (*21*). DIBOA could be prepared in this manner starting from 4-hydroxy-1,4-benzoxazin-3-one (**22**) by bromination (bromine in carbontetrachloride) and silver(I) carbonate assisted hydrolysis. Unfortunately, this method is not effective for the synthesis of DIMBOA. Bromination of 4-hydroxy-7-methoxy-1,4-benzoxazin-3-one (**21**) occurred exclusively on the aromatic ring at C-6 rather than at C-2, due to the activating nature of the 7-methoxy group. Similar results occurred when the bromination was performed with N-bromosuccinimide in acidic media.

N-Oxidation of Lactams Hydroxamic acids can also be produced by the oxidation of amides and lactams. Sammes (*22*) has reported the synthesis of DIBOA by the oxidation of the silylated lactam with a peroxo-molybdenum complex with dimethylformamide. The yield for the oxidation was 33%. This method can be used to overcome the limitations of the demethylation with boron trihalides; in particular it allows the synthesis of a 7-nitro analogue which would not be possible using the reductive cyclization/demethylation methods (*15,23*). In the event, the benzoxazinone ring is formed by condensation of the appropriate o-hydroxyaniline with dichloroacetylchloride followed by hydrolysis of the isolable dichloroacetanilide derivative to generate the 2-hydroxy-1,4-benzoxazin-3-one (Figure 3). Oxidation of the silylated derivative (formed by heating the lactam in neat bis(trimethylsilyl)acetamide) then forms the hydroxamic acid. Unlike the demethylations mentioned above, the yields for the N-oxidation of lactams decreased as the electron donating ability of ring substituents increased (Table II). This would seem to be a result of the substituent's effect on the silylation of the lactam. Sammes has shown that silylation of p-methoxyacetanilide gave predominantly N-silylated products and that p-chloroacetanilide was mostly O-silylated (*24*). It is only the O-silylated amides (O-silyl imino ethers) that are oxidized by the electrophilic peroxo-molybdenum complexes.

Chemical Reactivity

pka's and Unimolecular Decomposition The 2,4-dihydroxy-1,4-benzoxazin-3-ones decompose in organic and aqueous solvents to give benzoxazolinones with concomitant liberation of formic acid (*25,26*). For DIMBOA the major product of decomposition is MBOA. Figure 1 shows a proposed mode of decomposition for the un-ionized hydroxamic acid - the species expected in most organic solvents. The pH dependence of the rate of decomposition in aqueous solution describes a bell shaped curve with a maximum at pH 9, (*25*) the approximate pH of the larval lepidopteran gut (*27*). With the aid of the C-7 substituted analogues (**1**, **6**, **7**, **9**,

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

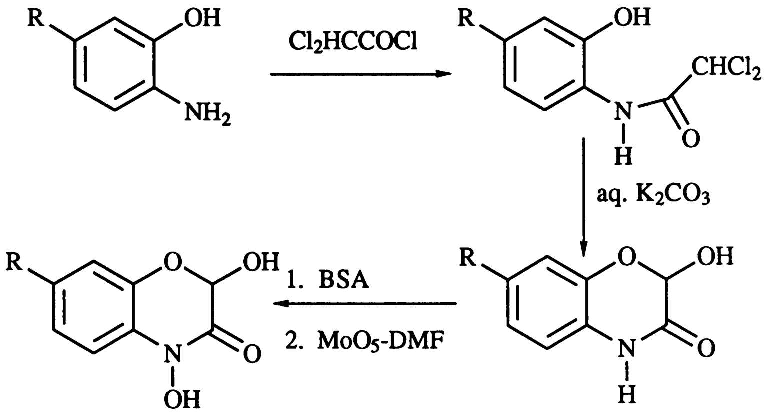
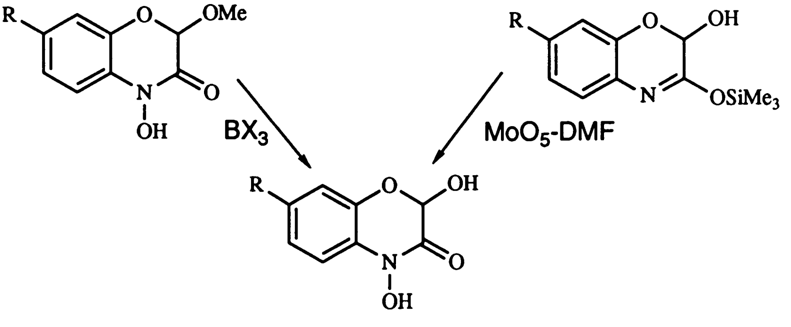

R
OH
NH2
Cl2HCCOCl
CHCl2
N
H
O
aq. K2CO3
1. BSA
2. MoO5-DMF

Figure 3. Synthesis of substituted 2-hydroxy-1,4-benzoxazin-3-ones and their oxidation to hydroxamic acids.

Table II. Comparison of isolated yields for the syntheses of lactol containing hydroxamic acids by demethylation and oxidation methodologies


R
OMe
O
N
OH
BX3
OSiMe3
MoO5-DMF

R	Percent Yields Demethylation	Oxidation
NO_2	no rxn	60
CN	no rxn	40
F	25	35
CH_3	96	10
CH_3O	70	< 5

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

10, **14**, and **16**) it has been possible to construct a linear-free-energy-relationship (LFER) for both pK_as (the hydroxamic acid and the lactol/phenol), as well as the observed pseudo-first-order rate constants for the decomposition (*15*).

When the pK_a of the hydroxamic acid ($pK_a{}^1$) is plotted versus the substituent constant σ_p a LFER is obtained with $\rho = 0.71$ (r^2=0.86, n=8). This is considerably higher than rho values reported for acylic N-phenyl substituted hydroxamic acids (ρ = 0.1)(*28*) and may be a result of the hydroxamic acid moiety being constrained in the benzoxazine ring structure. The second ionization, which actually represents the product of the dissociation constant of the phenol and the equilibrium constant of the lactol/phenol-aldehyde, also generates a LFER when plotted against σ_m. The ρ-value of 1.61 (r^2=0.85, n=8) resembles what one might expect for a phenol where the ρ–values are generally around two.

A less strict LFER exists for the rates of decomposition. The rates of decomposition were determined at specific pHs such that all compounds were ionized to the same degree. The 7-F and the 7-NO_2 compound could not be included in the relationship because of uncertain products in the 7-F case and because of poorly defined isosbestic points in the 7-NO_2 case. Recent work with the 7-NO_2 compound has shown that the decomposition is biphasic (*23*). 5-nitro-2-aminophenol was shown to be a product of the reaction suggesting that an intermediate carbamic acid is formed by attack of solvent water on an isocyanate. The nitro-group has changed the rate determining step of the decomposition and slowed the rate of intramolecular attack of the phenol on the isocyanate (Figure 1). For the remaining compounds a plot of log pseudo first-order rate constants versus σ^+, which takes into account resonance effects of the substituent, yields a LFER with $\rho = -1.1$ ($r^2 = 0.72$, n=6). The negative ρ-value means that, during the transition state for formation of the isocyanate, electron density at nitrogen decreases with respect to reactants.

Reaction Mechanism for Decomposition A number of mechanisms have been postulated to describe the decomposition of 2,4-dihydroxy-1,4-benzoxazin-3-ones to benzoxazolinones. They are of essentially two forms: (i) that the hydroxamic acid hydroxyl group is acting as an internal nucleophile,(*25*) or (ii) that it is a leaving group (*26,29*). Unfortunately, the present work does not distinguish between the two mechanisms since, in the LFER for the psuedo-first order rate constants of decomposition, the ρ–value of -1.1 describes a developing positive charge on nitrogen and this would be expected for both mechanisms as the N-O bond cleaves.

Reduction by Thiols The hydroxamic acid moiety of DIMBOA reacts with excess thiols in aqueous media to give the corresponding lactams as the main isolable product (*30*). For the reaction of DIMBOA with mercaptoethanol the pH dependence of the apparent second order rate constant, k^*_2, describes a bell-shaped curve with a maximum at pH approximately 8.3 and is kinetically described by the reaction of the unionized hydroxamic acid with the thiolate anion (*31*). This reduction reaction can be monitored spectrophotometrically since the hydroxamate anion and the product amide have different absorbance spectra. These studies with DIMBOA have been extended to include some of the analogues shown in **Table I** (*15*). It was found that only those compounds with electron rich aromatic rings were reduced at appreciable rates at 23° C. The methylenedioxy analogue **3** had the highest rate constant (6720 L mol-1 min-1 followed by **4** (1480), DIMBOA (**1**) (227) and **5** (88.5). It is not clear why the methylenedioxy ring of **3** affects the rate of reduction to such a degree since it is

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

doubtful that the electronic nature of the aromatic ring and the nitrogen atom are greatly different than in **4**. Clearly the C-6 oxy substituent is greatly enhancing the rate since the 7,8-dimethoxy substituted **5** is reduced more slowly than DIMBOA.

Aside from an electron rich aromatic ring, the lactol at C-2 is also necessary for facile reduction by thiol. Those analogues in which this functionality was blocked (**20**) or removed (**21**, **22**, and **24**) were not easily reduced. Small amounts of the lactams (<2-3%) could be detected by GC/MS if the conditions were forcing (excess thiol, 45°C, 16 hr), but most of the starting material remained. These experiments, combined with the observation by 1H-NMR that the aldehyde tautomer of those componds having a lactol were quickly titrated by the thiol to form hemithioacetals, suggested that only those analogues that could exist in a ring opened form (and that had electron rich aromatic rings) could be reduced by thiols in aqueous solution. A ring-opened structure would allow extended resonance between a methoxy substituent at C-7 and the partially positively charged nitrogen of a putative ion pair.

Mode of Action of Hydroxamic Acids in European Corn Borer

Feeding trials with laboratory cultures of the European corn borer have extended the work of Klun (32-35) and shown that DIMBOA increased larval mortality, decreased the pupal and adult weights, lengthened the time to pupation, and decreased the number of eggs and egg masses deposited by surviving adult females (*36*). Similar effects were found with MBOA (without the lowering of pupal and adult weights) but at much higher concentrations (*37*).

The nutritional indices of Waldbauer (*38*) have been utilized (*39*) to distinguish whether DIMBOA and MBOA manifest toxicity in a predigestive manner or postingestive (physiological effects taking place after crossing the gut wall). Studies with a range of concentrations have established that DIMBOA reduced the approximate digestibility and the efficiency of conversion of ingested food while MBOA reduced the efficiency of conversion of digested food . That is, DIMBOA manifested its effect as a larval toxin by interfering with digestive processes within the gut and MBOA, in some manner, affected the ability of the insect to utilize nutrients that have already been absorbed.

The log P values [log (octan-1-ol/water) partition coefficients] have been estimated for MBOA and un-ionized DIMBOA (*40*). Even when un-ionized, DIMBOA is more hydrophilic (log P=0.30) than MBOA (log P=0.91) and this difference would certainly be exaggerated at higher pH where DIMBOA is largely ionized. Consequently, assuming that DIMBOA is not actively transported across the gut wall at an appreciable rate, MBOA would more easily cross membrane barriers to other potential sites of interaction. Tracer studies with dietary 3H-DIMBOA or 3H-MBOA indicate in both cases that 3H-MBOA and other metabolites are detected in the insect internal tissues, while 3H-DIMBOA was not detectable in internal tissues after dietary administration (*40*).

Structure-Activity Relationships To date, feeding trials with *O. nubilalis* larvae have been conducted with most of the analogues in Table I except for **8**, **11**, **13**, **15**, **19** ($R_5 = H$ in Table I) and **16** and **18** which became available later. Table III compares the rates of reduction, rates of unimolecular decomposition, pK_as and growth inhibitory activity of the various analogues. Of the four compounds (**1**,**3-5**) that yielded kinetic results for reaction with mercaptoethanol, the two with the largest rate constants (**3** and **4**) did not inhibit the growth of larvae to an extent that was significantly different from control ($P<0.05$) Compounds **1** and **5** (DIMBOA and DIM_2BOA respectively, the aglucones of the naturally occurring 2-O-ß-D-glucosides) were less reactive towards reduction by mercaptoethanol but did inhibit growth,

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

DIM_2BOA to a lesser extent than DIMBOA. All of the 7-substituted series except for 7-CO_2Me, **14**, inhibited the growth of larvae during the feeding trials and all had activites equal to or surpassing that of DIMBOA. The remaining compounds tested (**2**, **20-24** and MBOA) did not significantly reduce growth.

Table III. Comparison of rates of reduction by mercaptoethanol, k_2, rate constants for unimolecular decomposition, k_{obs}, hydroxamic acid pK_a and growth inhibition in diets of *Ostrinia nubilalis*, for a series of cyclic hydroxamic acids

Compound		Reduction	Decomposition		
Number	Substituent	k_2 (M^{-1} min^{-1})[a]	k_{obs} (min^{-1})[b]	pK_a[1]	% Growth[c]
25	5-Me	---	$> 10^{-1}$		NS
3	6,7-MDO	6720	4.0×10^{-2}	6.91	NS
4	6,7-diMeO	1480	2.9×10^{-2}	6.91	NS
1	DIMBOA	227	8.6×10^{-3}	6.92	49
5	DIM_2BOA	88.5	7.2×10^{-3}	7.03	79
12	7-F	no rxn	9.0×10^{-3}	6.63	57
10	7-Cl	no rxn	3.0×10^{-3}	6.78	38
9	DIBOA	no rxn	$< 10^{-3}$	6.91	56
7	7-Me	no rxn	$< 10^{-3}$	6.83	27
6	7-*t*--Bu	no rxn	$< 10^{-3}$	6.94	53
14	7-CO_2Me	no rxn	$< 10^{-4}$	6.52	NS

a) True second order rate constants were obtained at 23 ± 0.3 ° C, pH 9.00 (Tris) and ionic strength 0.15. b) Pseudo first-order rate constants for unimolecular decomposition were determined at 37 ± 0.3 ° C, pH 9.00 (Tris-HCl) and ionic strength 0.15. c) Growth is expressed as percent of control. NS: not statistically different from control (χ^2 test, $\alpha = 0.10$). All compounds were tested at 0.5 mM in fresh meridic diets.

It is unlikely that the benzoxazolinones are responsible for a large measure of the biological activity of consumed hydroxamic acid since concentrations of MBOA ten to twenty times that of DIMBOA are necessary in feeding trials to show comparable toxicity. The rates at which the hydroxamic acids convert to benzoxazolinones, however, is likely very important. Hydroxamic acids that decompose in solution to produce less toxic benzoxazolinones more quickly than they react with nucleophiles on vital enzymes or proteins would not be expected to be active in an experiment such as a feeding trial. The diets for the feeding trials were made to approximately pH 4, a pH at which hydroxamic acids react or decompose very slowly at ambient temperatures. After three days in the diet nearly 70% of the added DIMBOA remained(*36*).

Once the hydroxamic acids are consumed and enter the high pH of the larval gut, the rates of reaction with nucleophiles and the rate of unimolecular decomposition to benzoxazolinones will compete. Compounds that are not hydroxamic acids (the lactams HMBOA and HBOA, **2** and **23**), or that have had the lactol blocked (**20**) or removed (**21**, **22** and **24**) did not inhibit the growth of the larvae in a manner significantly different from control. One might suspect then that those analogues which unimolecularly decay the slowest should have a greater opportunity to manifest toxicity. Table III compares the rate constants for reduction and decomposition reactions with growth inhibition as recorded during feeding trials. The pseudo-first order rate constants for decomposition given here do not represent the rate maxima for each compound since all measurements were made at pH 9.00 and the compounds have different pKa's. For the sake of comparison, the assumption has been made that pH 9 is near the maximum rate for all. Regardless of this assumption, all of the compounds would experience the same pH once ingested and present in the gut. It would seem that any compound which would unimolecularly decompose to benzoxazolinones with a rate constant greater than ≈2x10-2 min-1 at pH 9 does not persist long enough in the larval gut to manifest toxicity. Remarkably, DIMBOA and DIM_2BOA strike a balance between the different reactivities. They both decompose relatively fast in basic solution yet both are active in the growth study. They also represent the lower limit for reactivity towards reduction by mercaptoethanol. Those compounds that react faster with mercaptoethanol (**3** and **4**) decompose too quickly in solution, apparently, to show toxicity in the growth study. Compound **25** decomposes so fast at pH 9 that it was impossible to determine accurate absorbance data for it. The 7-CO_2Me analogue **14** is an anomaly since it undergoes unimolecular decomposition very slowly and yet showed no activity in the growth study. Perhaps the ester is hydrolysed in the insect gut and the revealed charged group (CO_2^-) interferes with the 'normal' toxicokinetics. It appears that the hydroxamic acid moiety and the lactol are necessary for activity, but there is no correlation between solution reactivity with mercaptoethanol and inhibition of the growth of *O. nubilalis* larvae. It is not possible with the information at hand to understand the variation within the growth inhibitory data.

Protease Inhibition Incubation of 3H-DIMBOA with partially purified trypsin from European corn borer, followed by gel filtration, showed that label co-eluted with protein. These protein containing fractions also had decreased proteolytic activity (*40*). Recent work (*39*) has shown that DIMBOA is an noncompetitive inhibitor of partially purified tryptic and chymotrypic activities from gut homogenates of the European corn borer. It is argued that an noncompetitive mode of inhibition would overcome the conditions of substrate saturation that exist in the gut of a feeding larva. DIMBOA has also been observed to inhibit in vitro the cysteine protease papain (*41*) and the serine protese α-chymotrypsin (*42*) by covalent interaction with the active site cysteine and serine respectively. Lower concentrations of DIMBOA were needed for inhibition of papain suggesting that the observed reactivity of DIMBOA and analogues with low molecular weight thiols may extend to proteins and enzymes as well. Further work is in progress to define the nature of enzyme inhibition and the events that affect larval fitness and mortality.

Role of Hydroxamic Acids in Crop Protection

Since the discovery of hydroxamic acids in corn and other cereal grains an extensive literature has developed correlating the occurrence and levels of these chemicals to plant resistance to insects herbivory and other pathogens (see ref. 11 and references therein). Varieties of maize with high contents of hydroxamic acids are resistant to the European corn borer and, as has been recently demonstrated, the western corn

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

rootworm (*Diabrotica virgifera virgifera* [LeConte]) (*8*). Thus, maintenance of sufficient hydroxamic acid levels in new maize cultivars should be an important concern in breeding programs. Interestingly, DIMBOA has also been identified as the agent responsible for poor growth of *Agrobacterium tumefaciens*, a bacterial vector being used to study the viability of transfecting genes responsible for herbicide resistance into corn (*43*). It has been suggested that it may be necessary to select plants with *low* DIMBOA content to allow this technology to procede. Hopefully other ways can be found to overcome these obstacles rather than to select against one of corn's demonstrably effective chemical defenses.

Conclusions

Synthetic methodologies now exist for the production of a variety of analogues of the general class of cyclic hydroxamic acids typified by DIMBOA. Generation of the hydroxamic moiety by reductive cyclization is limited to those aryl substituents that do not affect the ability of the boron trihalides to reveal the lactol. Oxidative generation of the hydroxamic acids from amides works best for strongly electron withdrawing aryl substituents and thus compliments the above method. The detailed mechanism of the unimolecular decomposition of DIMBOA and analogues is still not known, but clearly electron donating substituents such as methoxy greatly accelerate the reaction. Only four of the analogues were reduced by mercaptoethanol at appreciable rates (**1**, **3-5**) and feeding trials show that this reactivity does not correlate with the growth inhibitory activity in *O. nubilalis.* although several analogues had equal or better activity than DIMBOA. Work describing DIMBOA as a protease inhibitor, in conjuction with the known reactivity of the aldehyde tautomer of the lactol, suggests that both the hydroxamic acid and the aldehyde may play a role in association with macromolecules. This remains a goal of future work.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

Acknowledgments

The authors acknowledge the collaboration of Dr. N. Werstiuk (McMaster University, Hamilton) for preparation of tritiated MBOA and DIMBOA precursors, and Dr. J. Houseman (University of Ottawa) for helpful discussions concerning nutritional indices. JTA gratefully acknowledges funding from the Natural Science and Engineering Research Council (NSERC) and from the Ontario Ministry of Agriculture and Food (OMAF). HMN also acknowledges the Agency for International Development, International Program in the Chemical Sciences (Uppsala University) and FONDECYT for financial support.

Literature Cited

(1) Beck, S. D.; Stauffer, J. F. *Ann. Entomol. Soc. Am.* **1957**, *50*, 166-70.
(2) Smissman, E. E.; LaPidus, J. B.; Beck, S. D. *J. Org. Chem.* **1957**, *22*, 220.
(3) Loomis, R. S.; Beck, S. D.; Stauffer, J. F. *Plant Physiol.* **1957**, *32*, 379.
(4) Beck, S. D. *J. Insect Physiol.* **1957**, *1*, 158.
(5) Beck, S. D.; Smissman, E. E. *Ann. Entomol. Soc. Am.* **1961**, *54*, 53.
(6) Virtanen, A. L.; Hietala, P. K. *Acta Chem. Scand.* **1960**, *14*(2), 499-502.
(7) Brendenberg, J.-B.; Honkanen, E.; Virtanen, A. *Acta Chem. Scand.* **1962**, *16*, 35.
(8) Xie, Y. S.; Arnason, J. T.; Philogéne, B. J. R.; Lambert, J. D. H.; Atkinson, J. K.; Morand, P. *Can. Entomol.* **1990**, *122*, 1177-86.
(9) Thackray, D. J.; Wratten, S. D.; Edwards, P. J.; Niemeyer, H. M. *Ann. Appl. Biol.* **1990**, *116*, 573-82.

(10) Givovich, A.; Niemeyer, H. M. *Ent. Exp. Appl.* **1991**, *59*, 79-85.
(11) Niemeyer, H. M. *Phytochemistry* **1988**, *27*(11), 3349-58.
(12) Honkanen, E.; Virtanen, A. I. *Acta Chem. Scand.* **1960**, *14*(2), 504-7.
(13) Jernow, J. L.; Rosen, P. United States Patent 3,862,180, 1975.
(14) Coutts, R. T.; Hindmarsh, K. W. *Can. J. Pharm. Sci.* **1966**, *1*, 11-7.
(15) Atkinson, J.; Morand, P.; Arnason, J. T.; Niemeyer, H., M; Bravo, H. *J. Org. Chem.* **1990**, *56*(5), 1788-800.
(16) Hashimoto, Y.; Shudo, K.; Okamoto, T.; Nagao, M.; Takahashi, Y.; Sugimura, T. *Mutation Res.* **1979**, *66*, 191-194.
(17) Coutts, R. T.; Pound, N. J. *J. Chem. Soc. (C)* **1971**, 2696-2771
(18) Quiroz, A.; Niemeyer, H. M. *Heterocycles* **1991**, *32*, 1681-5.
(19) Johnstone, R. A. W.; Wilby, A. W.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*(2), 129-70.
(20) Corbett, M. D.; Chipko, B. R. *J. Chromatogr.* **1978**, *151*, 379-83.
(21) Sicker, D.; Prätorius, B.; Mann, G.; Meyer, L. *Synthesis* **1989**, 211-2.
(22) Matlin, S. A.; Sammes, P. G.; Upton, R. M. *J. Chem. Soc. Perkin I* **1979**, 2481-7.
(23) Bravo, H. R.; Niemeyer, H. M. *Heterocycles* **1991**, *32*, 1687-91.
(24) Matlin, S. A.; Sammes, P. G.; Upton, R. M. *J. Chem. Soc. Perkin I* **1979**, 2478-80.
(25) Bravo, H. R.; Niemeyer, H. M. *Tetrahedron* **1985**, *21*, 4983-6.
(26) Smissman, E. E.; Corbett, M. D.; Jenny, N. A.; Kristiansen, O. *J. Org. Chem.* **1972**, *37*(11), 1700-4.
(27) Dow, J. A. T. In "Advances in Insect Physiology"; Academic Press, Inc.: London, 1986; Vol. 19.
(28) Brink, C. P.; Crumbliss, A. L. *J. Org. Chem.* **1982**, *47*(7), 1171-6.
(29) Grambow, H. J.; Lückge, J.; Klausener, A.; Müller, E. *Z. Naturforsch.* **1986**, *41c*, 684-90.
(30) Niemeyer, H. M.; Corcuera, L. J.; Pèrez, F. J. *Phytochemistry* **1982**, *21*(9), 2287-9.
(31) Pèrez, F. J.; Niemeyer, H. M. *Phytochemistry* **1985**, *24*(12), 2963-6.
(32) Robinson, J. F.; Klun, J. A.; Guthrie, W. D.; Brindley, T. A. *J. Kansas Entomol. Soc.* **1982**, *55*(2), 357-64.
(33) Klun, J. A.; Robinson, T. A. *J. Econ. Entomol.* **1969**, *62*, 214-20.
(34) Klun, J. A.; Tipton, C. L.; Brindley, T. A. *J. Econ. Entomol.* **1967**, *60*, 1529-33.
(35) Klun, J. A.; Brindley, T. A. *J. Econ. Entomol.* **1966**, *59*, 711-8.
(36) Campos, F.; Atkinson, J.; Arnason, J. T.; Philogene, B. J. R.; Morand, P.; Werstiuk, N. H.; Timmins, G. *J. Chem. Ecol.* **1989**, *15*(7), 1989-2001.
(37) Campos, F.; Atkinson, J.; Arnason, J. T.; Philogène, B. J. R.; Morand, P.; Werstiuk, N. H.; Timmins, G. *J. Chem. Ecol.* **1988**, *14*(3), 989-1002.
(38) Waldbauer, G. P. *J. Insect Physiol.* **1968**, *5*, 229-88.
(39) Houseman, J. G.; Campos, F.; Thie, N. M. R.; Philogène, B. J. R.; Atkinson, J.; Morand, P.; Arnason, J. T. *J. Econ. Entomol.* **1991**. (in press)
(40) Campos, F. Ph.D. Dissertation, University of Ottawa, Ottawa, 1990.
(41) Pérez, F. J.; Niemeyer, H. M. *Phytochemistry* **1989**, *28*(6), 1597-600.
(42) Cuevas, L.; Niemeyer, H. M.; Pérez, F. J. *Phytochemistry* **1990**, *29*(5), 1429-32.
(43) Sahi, S. V.; Chilton, Mary-D.; Chilton, W. S. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 3879-83.

RECEIVED April 9, 1992

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch032

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Chapter 33

Nematicidal Activity of 5-Substituted-2-*S*-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles

Thomas G. Cullen, James M. Willut, Carmen P. DiSanzo[1], and Anthony J. Martinez[2]

Agricultural Chemical Group, FMC Corporation, P.O. Box 8, Princeton, NJ 08543

The 5-substituted-2-S-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles are effective in the control of root-knot nematode. In addition to excellent initial control, these compounds provide good residual control of the root-knot nematode. The strategy to optimize the control is discussed and a quantitative structure activity relationships (QSAR) model is presented. Finally, control of other nematode species is discussed.

The goal of our research program was to discover a nematicide which had good initial activity against the root-knot nematode, as well as residual control. Additionally, control of other economically important plant-parasitic nematodes, such as cyst, lesion and stunt nematodes was desired. Control of plant-parasitic nematodes, which are tiny but abundant soil-borne pests, is difficult and expensive. Nematodes are protected from many environmental stresses by their cuticle which withstands the penetration of many pesticides. The soil itself is a formidable barrier preventing many chemicals from penetrating to target sites efficiently, or degrading or inactivating them before they can reach sites of activity in concentrations sufficient to exert control. As a consequence, nematicides must be applied at relatively high rates and frequently hazardous concentrations to be minimally effective.

Chemical control of nematodes can be accomplished with two types of control agents. The first type are the fumigants which include the halogenated aliphatic hydrocarbons such as methyl bromide, 1,3-dichloropropene, 1,2-dibromoethane and chloropicrin. Methyl isothiocyanate derivatives, such as dazomet and metham sodium, are also considered fumigants. The other chemical class is the non-volatile contact materials. These materials are either organophosphates, such as fenamiphos, or carbamates, such as carbofuran.

A major disadvantage of all nematicides is their inherent toxicity coupled with the potential to be environmentally hazardous. As such, the development of new

---

[1] **Current address: Environmental Protection Agency, Pesticide Section, 841 Chestnut Building, Philadelphia, PA 19107**

[2] **Current address: Mercer County Community College, P.O. Box B, Trenton, NJ 08690**

0097–6156/92/0504–0361$06.00/0

nematicides was the goal of this research, but it was also realized that the costs to prepare and test new compounds were rising dramatically. Therefore, we concluded that if we used a rational design strategy to select synthesis targets at the beginning of a project, then we could identify the most active materials more rapidly, and be confident that active materials were not overlooked. By that, we meant that QSAR was to be used not as a retrospective analysis technique to understand properties contributing to biological activity, but it was to be used to direct our synthesis. Compounds containing the -S-(3,4,4-trifluoro-3-butenyl) fragment were known to impart significant nematicidal activity (*1-3*). The 5-substituted-2-S-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles, **1**, were one example of such compounds where a rational design strategy was used at the beginning of a project. The first step was the selection of targets, followed by synthesis and then determination of nematicidal activity. This biological data was analyzed to develop a QSAR model. The use of a rational design strategy before initializing synthesis has been shown to be an efficient method for the discovery and optimization of nematicidal activity.

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Set Selection

A set of 2-S-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles substituted at the 5-postion was designed to explore the physiochemical parameter space represented by π , σ, L and B1. In order to adequately cover the chosen parameter space, a 2^n factorial design was utilized (*4*). Austell suggests that a 2^n factorial design can be an objective method for selecting substituent sets (*5, 6*). Our choice of parameters represented the basic linear free energy parameters of lipophilicity, electronics and shape/size.

The selected compounds are shown in Table I. This group of compounds was examined to determine whether or not the physiochemical properties were cross-correlated. This set was found not to be cross-correlated (Table II), and it was confirmed that the selected compounds represented the design parameter space using factor analysis (*7*). With this method, an orthogonally arranged set afforded as many factors (Eigenvectors) as there were properties represented. In this case, all factors were separated which was desirable (Table III).

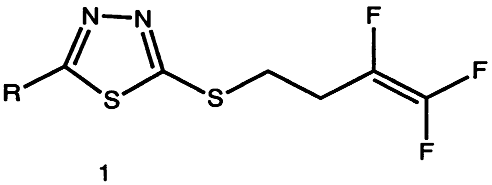
Target Synthesis

The synthesis of targets was accomplished as shown in the following schemes. Compounds were prepared from the commercally available 2,5-dimercapto-1,3,4-thiadiazole by treatment of this compound with either sodium hydride or sodium ethoxide to give the mercapto ion. The material was treated with 1-bromo-3,4,4-trifluoro-3-butene to give compound **9**. Compound **9** was used to prepare compounds **7**, **8**, **11** and **12** by the method of Martinez and Cullen (*2*) (Scheme 1).

The appropriate thioacylhydrazides, **17**, were treated with carbon disulfide to give the 2-mercapto-5-substituted-1,3,4-thiadiazoles, **18**. These materials were converted to desired materials using the synthesis route described in reference (*2*) (Scheme 2).

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Table I. Factorially Designed Analog Set



1

No.	R	Physicochemical Data			
		π	σ	L	B1
1	NH_2	-1.23	-0.66	2.93	1.50
2	$NH(C{=}O)C_6H_5$	0.49	-0.19	8.40	1.94
3	$C(CH_3)_3$	1.98	-0.20	4.11	2.59
4	H	0.00	0.00	2.06	1.00
5	OC_5H_{11}	2.04	-0.34	8.11	1.35
6	CL	0.71	0.23	3.52	1.80
7	SCH_3	0.61	0.00	4.30	1.70
8	SCH_2CCH	0.21	0.11	6.89	1.70
9	SH	0.39	0.15	3.47	1.70
10	C_6H_5	1.96	-0.01	6.28	1.70
11	SC_2H_5	1.07	0.03	5.24	1.70
12	$SCH(CH_3)_2$	1.40	0.07	4.95	1.70
13	$NH(C{=}O)CH_3$	-0.97	0.00	5.15	1.50
14	$CH_2C_6H_5$	2.01	-0.09	4.62	1.52
15	NHC_6H_5	1.37	-0.40	4.53	1.50
16	NHC_2H_5	0.08	-0.61	4.96	1.50

Variable	Smallest Value	Largest Value
1 π	-1.2300	2.0400
2 σ	-0.6600	0.2300
3 L	2.0600	8.4000
4 B1	1.0000	2.5900

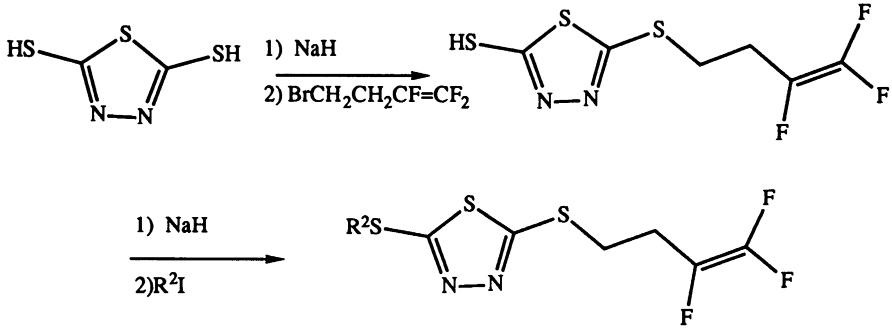
Table II. Correlation Matrix for Analog Set

Parameters		π	σ	L	B1
		1	2	3	4
π	1	1.000			
σ	2	0.163	1.000		
L	3	0.324	-0.050	1.000	
B1	4	0.325	0.134	0.160	1.000

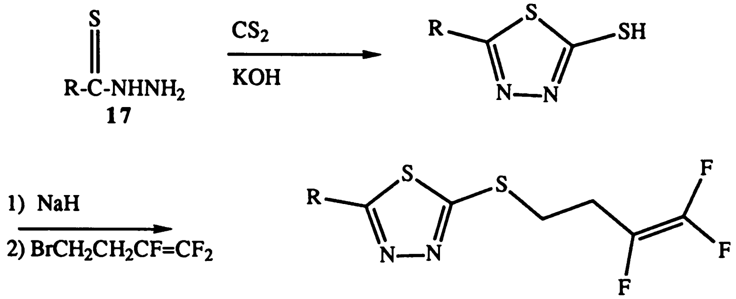
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Table III. Factor Analysis for Analog Set

Parameters	Factor 1	Factor 2	Factor 3	Factor 4
L	0.984	0.000	0.000	0.000
B1	0.000	0.983	0.000	0.000
σ	0.000	0.000	0.995	0.000
π	0.000	0.000	0.000	0.970
VP	1.002	1.002	1.001	0.995



Scheme 1. Preparation of Dithio-1,3,4-thiadiazoles



Scheme 2. Preparation of Remaining Synthesis Targets

Biological Testing

Compounds were formulated as dust formulations (5% active ingredient) for determination of initial and residual activity. The activity against root-knot nematode *(Meloidogyne incognita)* was determined by incorporating the formulated test compound in nematode-infested soil at rates in the range of 10 ppm to 0.078 ppm. A cucumber seedling was planted in the treated nematode infested soil. Two weeks after planting, the test pots were evaluated to ascertain the degree of galling (swelling) on

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

the roots of the plants, indicating the control provided by the test chemical (*8*). From the percent control at each rate the LC_{50} was determined.

The residual root-knot nematicidal activity was evaluated by incorporating dust formulations (5% active ingredient) of the compound into uninfested soil at test rates of 5 and 10 ppm. The soil treated with test compound was placed in 7.6 cm diameter fiber pots and held in a greenhouse. At one, two and four weeks post-treatment, the appropriate number of pots were infested with root-knot nematode eggs and larvae. A cucumber or tomato seedling was planted in each pot and evaluated at two weeks as described above. The test results are reported as percent control at each rate tested.

Activity against three additional nematode species was determined. The stunt nematode (*Tylenchorhynchus claytoni*) test procedure was essentially the same as in the initial root-knot nematode tests described above, except that the rates of application of formulated compound (5% dust active ingredient) were 2.5 and 5 ppm in soil containing a corn seedling, and the subsequent inoculation of the soil combined larvae and adult stunt nematodes. The pots were evaluated approximately four weeks after infestation. The percent control was determined by extracting the nematodes from the soil and counting the number in treated versus untreated pots. The lesion nematode (*Pratylenchus penetrans*) test procedure was essentially the same as in the stunt nematode test described above except that pea seedlings were used and nematodes present in soil and in roots were determined. The cyst nematode (*Heterodera glycines*) test was the same as described in the stunt nematode test, except soybean seedlings were used.

Structure Activity Relationships

The sixteen compounds of our analog set were prepared and the initial root-knot activity was determined (Table IV). This data was reported as an LC_{50} in parts per million and converted to the negative $Log(LC_{50})$. Our first analysis, shown in equation 1, was a disappointment. From this, only one variable was statistically significant, that is, σ with a r^2 of 0.33 (r=0.575). It was realized that a factorial design was not a complete design, such as a central composite design, and it was possible to translate the center point of our design to one of the more active compounds in our original analog set. Compound **11** was chosen as the center point of a new half fractional design. The physiochemical data is shown in Table V; the correlation matrix in Table VI and the factor loadings in Table VII. It was evident from Table VI and Table VII that our new design represented the chosen physiochemical properties. Equation 2 was the result of this new analysis. As this shows, the two significant parameters were sigma and π, with an r^2 of 0.82 (r=0.906).

$$-Log(LC_{50}) = -0.05 + 1.15\ (\pm 0.437)\ \sigma \qquad (1)$$

$n = 16 \quad r = 0.575 \quad s = 0.445 \quad F = 6.914$
$(p = 0.020)$

$\sigma \quad t = 2.63 \quad (p = 0.02) \quad (-0.66 - 0.23)$

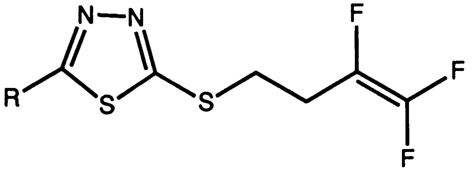
$$-Log(LC_{50}) = -0.14 + 1.78\ (\pm 0.39)\ \sigma + 0.19\ (\pm 0.12)\ \pi \qquad (2)$$

$n = 8 \quad r = 0.906 \quad s = 0.264 \quad F = 11.530$
$(p = 0.013)$

$\sigma \quad t = 4.56 \quad (p = 0.01) \quad (-0.61 -0.15)$
$\pi \quad t = 1.66 \quad (p = 0.16) \quad (0.08 - 2.04)$

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Table IV. Initial Root-knot Biological Data



1

No.	R	LC_{50} (ppm)*	$\log(LC_{50}^{-1})$
1	NH_2	1.8	-0.24
2	$NH(C{=}O)C_6H_5$	1.5	-0.17
3	$C(CH_3)_3$	2.1	-0.32
4	H	2.5	-0.40
5	OC_5H_{11}	1.9	-0.27
6	CL	3.1	-0.49
7	SCH_3	0.4	0.42
8	SCH_2CCH	1.4	-0.15
9	SH	0.7	0.16
10	C_6H_5	1.1	-0.02
11	SC_2H_5	0.2	0.63
12	$SCH(CH_3)_2$	0.2	0.65
13	$NH(C{=}O)CH_3$	1.7	-0.23
14	$CH_2C_6H_5$	1.3	-0.10
15	NHC_6H_5	15	-1.17
16	NHC_2H_5	17	-1.24

The next question that we asked ourselves was could we separate the sigma term into its field (F) and resonance (R) contributions? As before, we had to determine whether F, R and π were well represented and whether the factors were separated. Table VIII and Table IX show the correlation matrix and the factor loadings, respectively. The examination of this output revealed that the parameters were independent of each other. Equation 3 was significant with an r^2 of 0.78 ($r=0.884$), wherein the contribution of field and resonance effects to nematicidal activity has been shown. However, we felt that equation 2 was the better model for understanding nematicidal activity in a soil environment, as it contained both an electronic component and a lipophilic component.

$$-\mathrm{Log}(LC_{50}) = -0.09 + 2.25\ (\pm 0.66)\ F + 1.38\ (\pm 0.53)\ R \qquad (3)$$

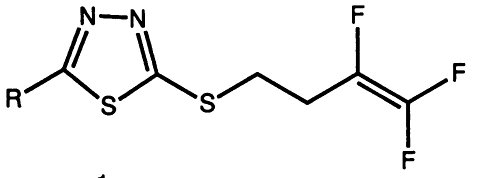
$n = 8$ $r = 0.884$ $s = 0.293$ $F = 8.949$ $(p = 0.022)$

F $t = 3.40$ $(p = 0.02)$ $(-0.11 - 0.28)$
R $t = 2.62$ $(p = 0.05)$ $(-0.57 - -0.01)$

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Table V. Translated Set of Analogs



1

		Physiochemical Data					
No	R	π	σ	F	R	L	B1
2	$NH(C{=}O)C_6H_5$	0.49	-0.19	0.09	-0.27	8.40	1.94
3	$C(CH_3)_3$	1.98	-0.20	-0.07	-0.13	4.11	2.59
4	OC_5H_{11}	2.04	-0.34	0.25	-0.57	8.11	1.35
8	SCH_2CCH	0.21	0.11	0.16	-0.03	6.89	1.70
9	SH	0.39	0.15	0.28	-0.11	3.47	1.70
12	$SCH(CH_3)_2$	1.40	0.07	0.28	-0.19	4.95	1.70
14	$CH_2C_6H_5$	2.01	-0.09	-0.08	-0.01	4.62	1.52
16	NHC_2H_5	0.08	-0.61	-0.11	-0.51	4.96	1.50

Variable	Smallest Value	Largest Value
1 π	0.0800	2.0400
2 σ	-0.6100	0.1500
3 L	3.4700	8.4000
4 B1	1.3500	2.5900

Table VI. Correlation Matrix for Translated Analog Set

Parameters		π	σ	L	B1
		1	2	3	4
p	1	1.000			
s	2	-0.033	1.000		
L	3	-0.063	-0.220	1.000	
B1	4	0.154	0.129	-0.253	1.000

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Table VII. Factor Loadings for Translated Analog Set

Parameters		Factor	Factor	Factor	Factor
		1	2	3	4
σ	2	0.992	0.000	0.000	0.000
π	1	0.000	0.997	0.000	0.000
B1	4	0.000	0.000	0.987	0.000
L	3	0.000	0.000	0.000	0.986
	VP	1.001	1.000	1.000	0.999

Table VIII. Correlation Matrix of Electronic and Lipophilic Parameters

		Physiochemical Data		
Parameters		π	F	R
		1	2	3
π	1	1.000		
F	2	-0.078	1.000	
R	3	0.022	-0.031	1.000
Variable			Smallest Value	Largest Value
1 π			0.0800	2.0400
2 F			-0.1100	0.2800
3 R			-0.5700	-0.0100

Table IX. Factor analysis for F, R and MR

Parameters		Factor	Factor	Factor
		1	2	3
R	3	1.000	0.000	0.000
π	1	0.000	0.999	0.000
F	2	0.000	0.000	0.999
	VP	1.000	1.000	1.000

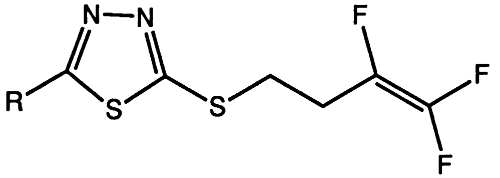
Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Nematicidal Evaluations

The control of root-knot nematodes was our primary goal. It was known that while good initial activity was necessary, it was not sufficient. Residual control of root-knot nematode was needed.

Accordingly, compounds **7** and **11** were selected for residual testing and the percent control was determined at seven days, 14 days and 28 days (Table X). From this test it was found that compound **11** gave nearly complete control at 28 days, while compound **7** was ineffective after seven days. In addition, compounds **7** and **11** were tested against the cyst, lesion and stunt nematodes (Table XI). While these materials provided initial control of these nematode species, it was marginal. For example, compound **11** provided only fifty percent control of cyst and stunt nematodes in these tests.

Table X. Residual Activity Against Root-knot (Percent Control at 5 ppm)



Compound	R Group	7 days	14 days	28 days
7	SCH_3	97	38	43
11	SC_2H_5	98	97	95

Table XI. Percent Control of Nematode Species (Rate = parts per million (ppm))

	Species		
R Group	Cyst (5 ppm)	Lesion (2.5 ppm)	Stunt (5 ppm)
SCH_3	70	-	65
SC_2H_5	52	72	53

Conclusions

The use of a design strategy to choose the original set for synthesis has been shown to be an effective method to optimize lead activity. In our case, 5-substituted-2-S-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles were found to be effective, broad spectrum nematicides. The use of a rational design set allowed us to identify the more active analog quickly and efficiently. Furthermore, fewer compounds required evaluation in spectrum and residual tests, as we were confident that the more active materials were included based on the results of our QSAR analyses. However, the 5-substituted-2-S-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles were not sufficiently active in residual and spectrum tests to warrant further development as nematicides.

Acknowledgments

The authors would like to acknowledge the contributions of our many co-workers in this program, Edward J. Barron, Patricia L. Morris and Patricia J. Aikens prepared many of the compounds discussed; Michael J.Bonner and Russel J. Savage performed the nematode evaluations. Susan A. Meissner aided in manuscript preparation. Finally, the authors acknowledge the support of FMC Corporation.

Literature Cited

1. Brokke, M. E.; (Stauffer Chemical Co.) U. S. Patent 3,513,172, 1970.
2. Martinez, A. J.; Cullen, T. G.; (FMC Corporation) U. S. Patent 4,952,580, 1990.
3. Cullen, T. G.; Martinez, A. J.; Vukich, J. J.; (FMC Corporation) U. S. Patent 4,748,186, 1988.
4. Austel, V.; *Eur. J. Med. Chem., 17,* **(1982)**, 9.
5. Austel, V.; *Eur. J. Med. Chem., 17,* **(1982)**, 339.
6. Austel, V.; *In Quantitative Approaches to Drug Design*, Edited by Dearden, J. C.; Elsevier Science Publishers: Amsterdam, 1983.
7. Martin, Y. C.; Panas, H. N.; *J. Med. Chem., 22*, **(1979)**, 784.
8. Barker, K. R.; Townshend, J. L.; Bird, G. W.; Thomson, I. J.; Dickson, D. W.; *In Methods for Evaluating Pesticides for Control of Plant Pathogens*; American Phytopathological Society Press, Minneapolis, 1986.

RECEIVED July 6, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch033

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

Chapter 34

Fungicidal β-Methoxyacrylates

From Natural Products to Novel Synthetic Agricultural Fungicides

John M. Clough, Paul J. de Fraine, Torquil E. M. Fraser, and Christopher R. A. Godfrey

ICI Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY, United Kingdom

A knowledge of the structures and properties of the fungicidal natural products strobilurin A and oudemansin A has led to the discovery of a new class of agricultural fungicides containing the (*E*)-methyl β-methoxyacrylate group with high levels of broad spectrum fungicidal activity and a good persistence of effect.

The quest for new agricultural fungicides is motivated by several important factors. Firstly, it is becoming increasingly desirable to replace existing products with compounds of lower toxicity to non-target species and with acceptable levels of persistence in the environment. Secondly, in order to remain competitive, agrochemical companies are obliged to look for new compounds which show marketable advantages over existing products in terms of efficacy and breadth of spectrum. These chemicals can often be protected with patents which prevent access by competitors for a limited period. Finally, the development of fungicides with novel modes of action is an important strategy in the search for ways to overcome cross-resistance to established products.

The discovery of new fungicide leads has been achieved in several different ways, including the random screening of compounds, the design of inhibitors of vital biochemical processes and the exploitation of loop-holes in competitors' patents. Natural products with fungicidal activity represent a pool of structurally diverse compounds which can offer the chemist an attractive starting point for synthesis. However, with a few notable exceptions [such as pyrrolnitrin (*1*)], examples which have led to the development of new fungicides are rare.

This account describes how a consideration of the chemical and physical properties of the natural products strobilurin A and oudemansin A has led to the discovery of a new class of synthetic fungicides containing the (*E*)-methyl β-methoxyacrylate group with high levels of broad spectrum activity and a good persistence of effect. A more detailed account of the initial stages of this work has recently been published (*2*).

0097–6156/92/0504–0372$06.00/0

Natural β-Methoxyacrylates as Leads for Synthesis

Strobilurin A and oudemansin A (Figure I) are the simplest members of a family of fungicidal natural products (now totalling sixteen compounds) which contain the (*E*)-methyl β-methoxyacrylate group, most of which are derived from the mycelia of various Basidiomycete fungi of European origin.

We first became interested in these compounds in 1981 following a publication by Steglich and co-workers, which drew together for the first time the structures of three β-methoxyacrylates (strobilurins A and B and oudemansin A) and the related compound myxothiazol (*3*). In spite of the obvious structural differences of myxothiazol, these compounds all share a common mode of action and can therefore be said to be biochemically equivalent. Indeed, it has now been established that they inhibit fungal respiration by binding strongly to a specific site on cytochrome b, thereby preventing electron transfer between cytochromes b and c_1.

The modest fungicidal activity reported for these compounds, coupled with their potentially resistance-breaking mode of action, combined to make this an attractive area for synthesis. Furthermore, a knowledge of the mode of action meant that it would be possible to set up an *in vitro* assay which could be used to direct the synthesis of analogues. The potential of a respiration inhibitor for mammalian toxicity was also recognised at the outset, but this was not considered to be a fatal negative at this early stage. Later results supported this conclusion (see below).

However, before committing ourselves to any synthetic work, we felt that it was necessary to confirm the reported fungicidal activity of the natural products on our own biological screens. Although we were initially unable to obtain a sample of strobilurin A, Prof. Anke (University of Kaiserslautern, FRG) and Dr. Reichenbach (GBF, Braunschweig, FRG) kindly furnished us with samples of oudemansin A and myxothiazol, respectively. Both compounds subsequently showed good *in vivo* activity in the glasshouse at 33ppm against a range of commercially important fungi.

The Total Synthesis of Strobilurin A

In view of its perceived importance as the simplest member of the group, the decision was then taken to prepare a sample of strobilurin A. Initial work aimed at the preparation of the compound with the published (*all-E*)- configuration established that the structure of the natural product had been incorrectly assigned and that the correct assignment was probably (*E,Z,E*), as shown in Figure I. The geometry was finally confirmed by an unambiguous synthesis starting from a dienoate of known configuration (*4*).

Conformational analysis of the structure of strobilurin A using a combination of molecular mechanics and molecular orbital calculations showed its minimum energy conformation to be comprised of two planar portions (the phenylpentadienyl and the β-methoxyacrylate groups) positioned orthogonal to each other. Interestingly, although the central unit of oudemansin A is rather different, in that it has two adjacent chiral sp^3 centres in place of the (*Z*)-olefinic bond of strobilurin A, the published single crystal X-ray structure indicates that the overall shape is very similar (*5*). It is therefore not necessary to postulate that oudemansin A is a biological precursor (*via* loss of methanol) to strobilurin A. By contrast, (*all-E*)-strobilurin A is radically

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

different in terms of overall shape, thus providing further evidence for the (*E*,*Z*,*E*)-geometry of the natural product.

With a sample of strobilurin A in hand, we were able to test for fungicidal activity. The result turned out to be very disappointing, bearing in mind the earlier results obtained for oudemansin A and myxothiazol, since the compound was essentially inactive against fungi growing on whole plants in the glasshouse. By contrast, *in vitro* tests carried out in subdued light on fungi growing on agar were positive and biochemical studies using mitochondria isolated from beef heart confirmed that the compound was a potent inhibitor of respiration. Following laboratory tests using thin films of the compound on glass plates and a xenon lamp to simulate sunlight, we concluded that photochemical instability was the reason for the inactivity of strobilurin A *in vivo*. Later work established that loss through volatilisation was also a contributing factor.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

Analogues of Strobilurin A and Oudemansin A

This information prompted us to pursue the synthesis of analogues with improved photostability. It seemed reasonable that the characteristic β-methoxyacrylate group, present in virtually all of the natural products, was important for activity ("the toxophore") and that the rest of the molecule (the phenylpentadienyl moiety in the case of strobilurin A) might be functioning as a "carrier group" for the toxophore and so would be amenable to further modification. If this was the case, we felt that it should be possible to replace the carrier group with other lipophilic groups of greater photochemical stability. The activity of oudemansin A reassured us that the β-methoxyacrylate group was unlikely to be of limiting photochemical stability.

Figure II illustrates some of the compounds which were made to test this hypothesis. The first idea was to remove some or all of the unsaturation in the carrier group. The resulting compounds **1** and **2** were clearly flexible enough to adopt the shape of the natural products, but neither compound was active in the glasshouse (although the styrene **2** did show some activity *in vitro*).

A second approach was to replace the central unit with a relatively stable amide bond to produce an analogue such as **3**. In this case, the conformer required to mimic the shape of the natural products (as shown) was calculated to be the preferred one. This was more successful in terms of observed *in vivo* activity, but scope for further structural modification turned out to be limited.

Of far greater promise was the idea of freezing the geometry of the potentially labile (*Z*)-double bond of strobilurin A by fixing it within a benzene ring. The resulting stilbene **4** was readily prepared and was shown to have very good broad spectrum activity in the glasshouse (*6*). Consistent with this result was the improved photostability of this compound in comparison with strobilurin A in our laboratory tests.

The results of the tests indicated that strobilurin A decomposed very rapidly in artificial sunlight [photochemical T_{50} (film) = 1 minute] , whereas stilbene **4** was significantly (but not dramatically) longer lived [photochemical T_{50} (film) = 3 minutes] (Figure III; T_{50} is the time taken for the loss of the first 50% of the material under test). This also supported the idea that the reduced volatility of the stilbene **4** with respect to the natural product was also contributing to its much better performance in the glasshouse.

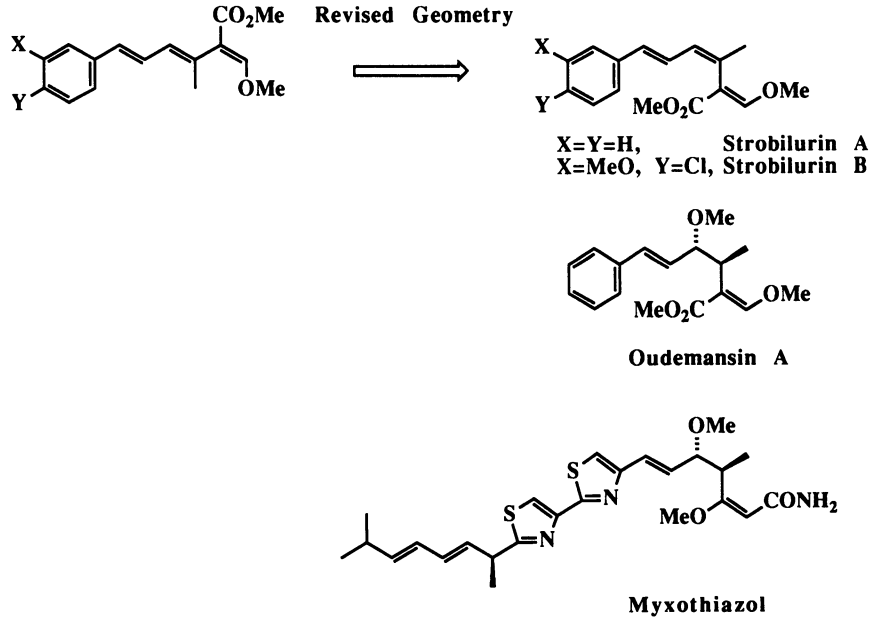

CO2Me
Revised Geometry
X
Y
OMe
X
Y
MeO2C
OMe
X=Y=H, Strobilurin A
X=MeO, Y=Cl, Strobilurin B
OMe
MeO2C
OMe
Oudemansin A
OMe
S
N
S
N
MeO
CONH2
Myxothiazol

Figure I : Natural Fungicidal Derivatives of β-Methoxyacrylic Acid

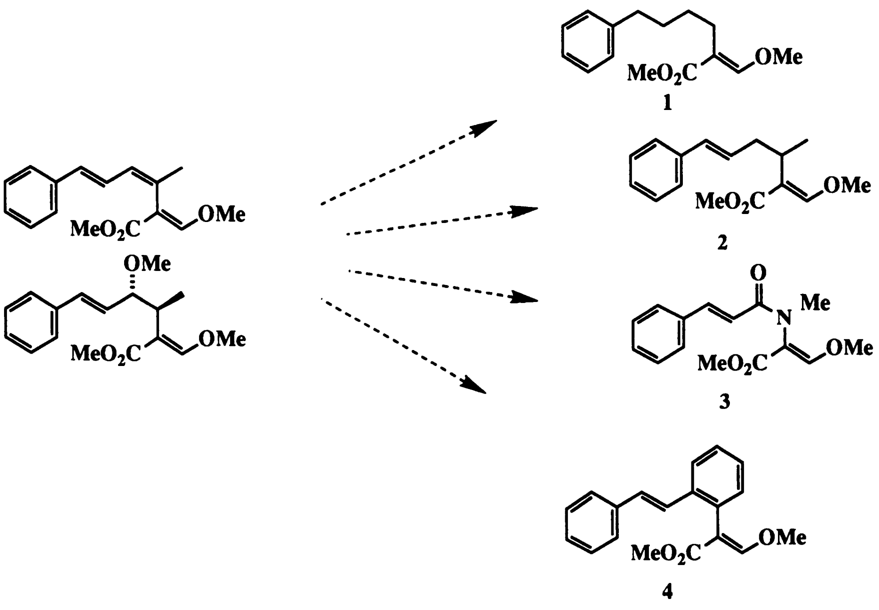

MeO2C
OMe
OMe
MeO2C
OMe
MeO2C
OMe
1
MeO2C
OMe
2
O
N
Me
MeO2C
OMe
3
MeO2C
OMe
4

Figure II : Analogues of Strobilurin A and Oudemansin A

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

Disappointingly, limited trials with the stilbene **4** showed that it was much less active in the field than was forecast from the glasshouse studies and this was attributed to the fact that its photostability was still less than ideal. The incorporation of an adjuvant which could function as an ultraviolet filter in the formulation was consequently examined as a possible means of further stabilising the stilbene **4** under field conditions. Of about 10 such compounds tried, Tinuvin 327 was found to be the most effective at increasing the stilbene's persistence in the laboratory (Figure III), but translation of this effect to the field proved to be impracticable.

Further Photochemical Degradation Studies

Clearly, the addition of a filter was not the way forward and so we looked in more detail at the fate of the stilbene **4** on irradiation. Since the use of thin films gave no identifiable products, we turned our attention to the photolysis of solutions of the compound in dichloromethane. Under these conditions, irradiation with a "Hanau suntest" lamp led to the formation of the naphthalene derivative **5**, which is presumably formed *via* the electrocyclic process shown in Figure IV.

This result suggested the synthesis of analogues such as **6** and **7** possessing extra substituents designed to disfavour the conformation required for decomposition by this pathway. In fact, the dichlorinated analogue **6** was even less stable than the parent stilbene **4** and poorly active, whereas the methylated derivative **7**, although more stable photochemically, suffered a significant drop in activity when compared to stilbene **4**. A far better approach was again to freeze the olefinic bond of the stilbene in the required (*E*)-configuration within a benzene ring. We therefore prepared the corresponding phenyl substituted naphthalene derivative **8**, which proved to be much more stable to light and highly fungicidal (*7*).

Replacement of the Styryl Group with a Phenoxy Group

A much simpler idea, however, both conceptually and synthetically, was to replace the offending styryl group of stilbene **4** with groups which could not participate in the observed decomposition pathway. In practice, many different side-chains can be used (see Figure V, for example) and in some cases fungicidal activity is substantially improved.

More surprising was the observation that the readily prepared diphenyl ether **9** (Figure VI) (*6*), which maps much less effectively onto strobilurin A than the stilbene **4**, showed dramatically increased stability to light [photochemical T_{50} (film) = 30 hours] and good levels of fungicidal activity against a range of commercially important and taxononomically diverse fungi (*6*). Some of the key physical properties of the diphenyl ether **9** are shown in Figure VI, while Table I shows the results of 24 hour protectant tests (foliar spray/root drench) *vs. Puccinia recondita* (brown rust on wheat, a Basidiomycete), *Plasmopora viticola* (vine downy mildew, a Phycomycete), *Venturia inaequalis* (apple scab, an Ascomycete) and *Pyricularia oryzae* (rice blast, a Deuteromycete). In the last case the observed activity was as good as the commercial standard.

Prior to field testing, the diphenyl ether **9** was also put through a battery of simple tests to detect mammalian toxicity and the results were very favourable. The acute oral toxicity (median dose, male and female rat) was greater than 500mgkg^{-1} and

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

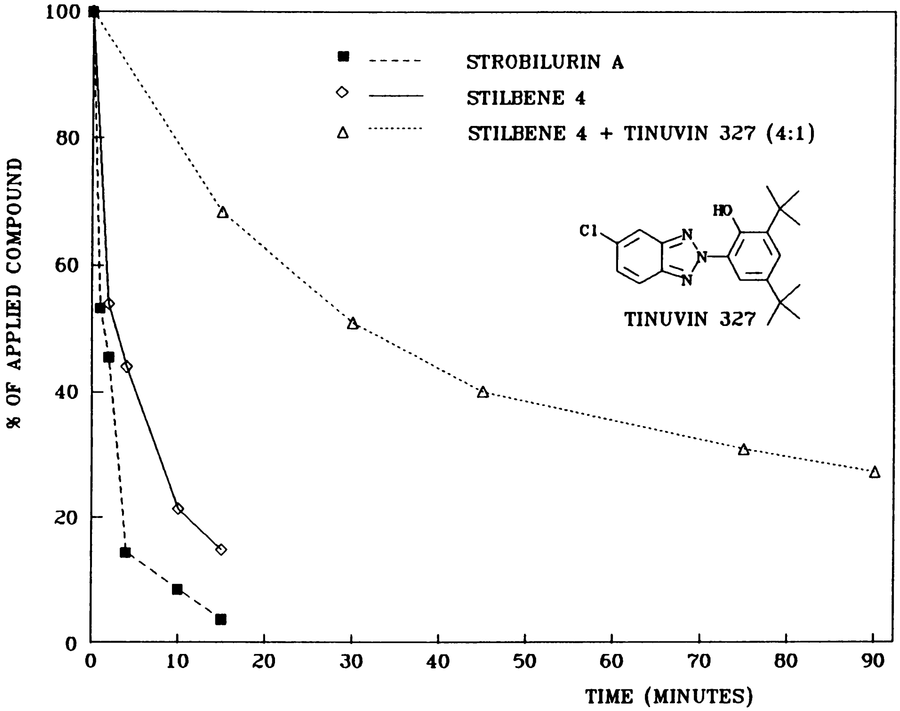
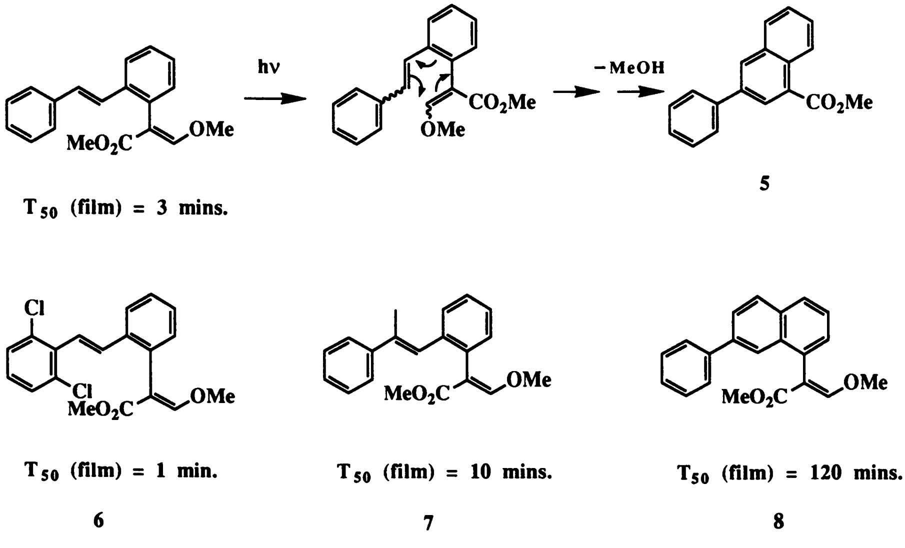


Figure III : Photochemical Degradation of Strobilurin A and Stilbene 4


MeO2C
OMe
hν
CO2Me
OMe
−MeOH
CO2Me
Cl
Cl
MeO2C
OMe
MeO2C
OMe
MeO2C
OMe

T_{50} (film) = 3 mins.

5

T_{50} (film) = 1 min.

6

T_{50} (film) = 10 mins.

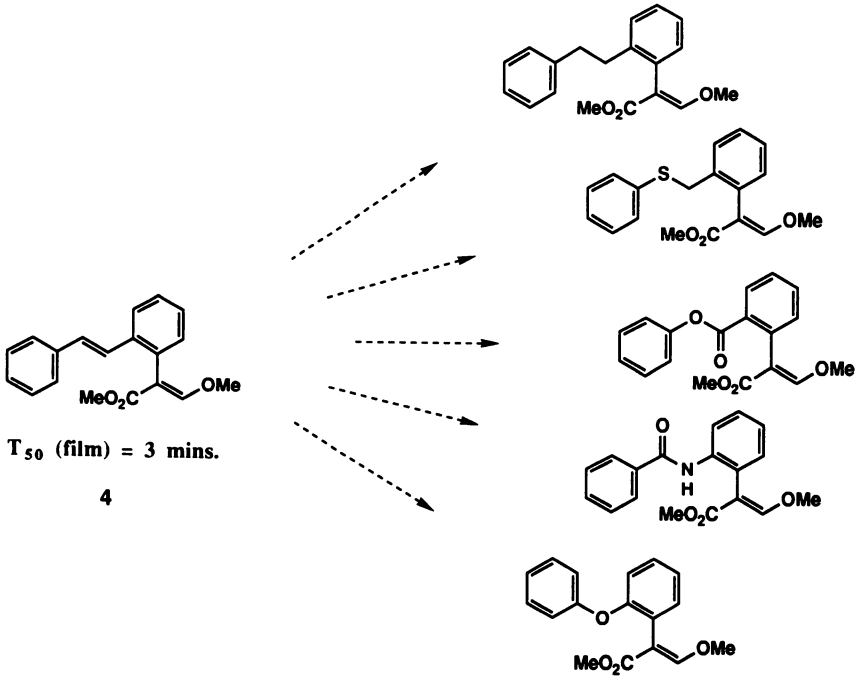
7

T_{50} (film) = 120 mins.

8

Figure IV : Photochemical Degradation of Stilbene 4

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034



T$_{50}$ (film) = 3 mins.

4

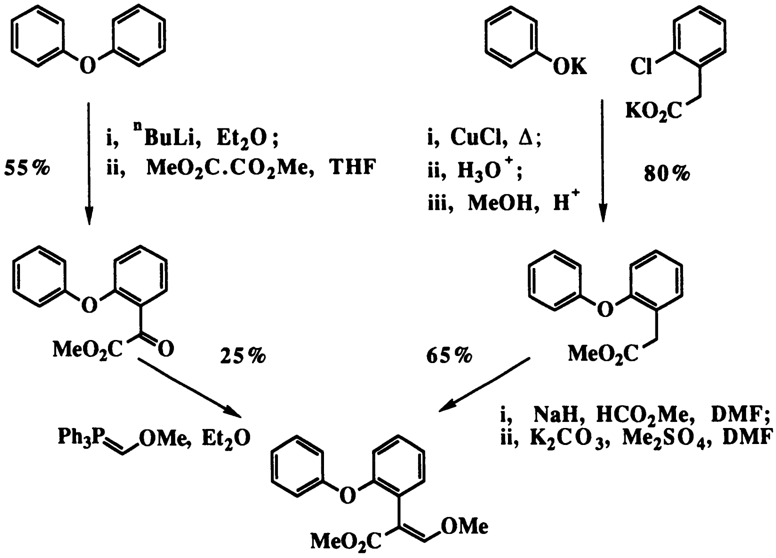
T$_{50}$ (film) = 30 hours

9

Figure V : Replacements for the Styryl Group

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034


55%
i, ⁿBuLi, Et₂O ;
ii, MeO₂C.CO₂Me, THF
OK
Cl
KO₂C
i, CuCl, Δ;
ii, H₃O⁺;
iii, MeOH, H⁺
80%
O
MeO₂C
O
25%
65%
MeO₂C
Ph₃P OMe, Et₂O
i, NaH, HCO₂Me, DMF;
ii, K₂CO₃, Me₂SO₄, DMF
MeO₂C
OMe

9

Melting Point = 41-3°C

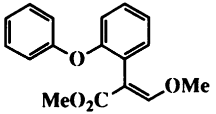
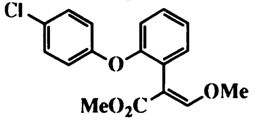
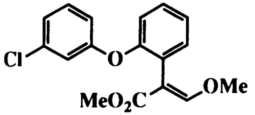
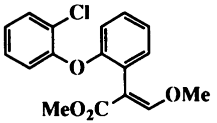
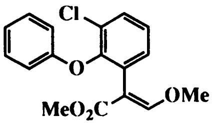
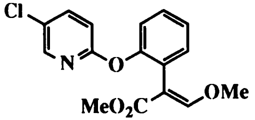
Log P (octanol/water) = 3.3

Water-Solubility (room temp.) = 30ppm

Figure VI : Synthesis of Diphenyl Ether 9

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

Table I

Compound	*Puccinia recondita*		*Plasmopara viticola*		*Venturia inaequalis*		*Pyricularia oryzae*	
	Foliar	Root	Foliar	Root	Foliar	Root	Foliar	Root
 9	*	*	*	-	*	*	**	*
 13	≥*	-	-	-	≥*	-	-	-
	≥*	-	≥*	-	≥*	-	*	-
	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-
 12	**	**	**	*	*	≥*	*	**

- Weak activity * Moderate activity ** Activity ≥ Commercial standard the compound was neither a strong skin sensitiser nor a skin irritant. Furthermore, it gave a negative result in the Ames' test.

In the field, the diphenyl ether **9** showed encouraging activity at 750gha^{-1}, equalling the standards (at their commercial rates) against *Puccinia recondita, Erysiphe graminis* (powdery mildew on wheat and barley) and *Septoria nodorum* (glume blotch on wheat) and showing some activity against *Rhynchosporium secalis* (leaf blotch on barley). However, in several (but not all) of the trials some crop damage was also observed.

These promising results represented both the culmination of our efforts to improve the photostability of the natural products and the starting point for all of our subsequent work on the optimisation of physical and biological properties of synthetic analogues in the diphenyl ether area. The main objectives of this work were to attain higher levels of activity in the field and to reduce the phytotoxicity to an acceptable level.

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

Diphenyl Ether Analogues

First of all, in order to confirm that the *ortho*-phenoxy substituent of the diphenyl ether **9** was in the optimum position, we prepared the two possible regioisomers **10** and **11**. The results from our screens clearly demonstrated that fungicidal activity falls off very sharply as the phenoxy group is moved around the ring, which was consistent with the modelling studies that we had carried out earlier. The validity of the model was further supported by the results of testing the corresponding stilbene analogues (regioisomers of the stilbene **4**).

We next looked at the effect of chlorination of the phenoxy substituent and discovered that whereas *meta*- and *para*-substitution retained activity, an *ortho*-substituent caused a significant drop in activity (Table I). Similarly, introduction of a chlorine substituent into the ring bearing the β-methoxyacrylate group at the position *ortho* to the phenoxy-substituent reduced activity sharply. The most obvious explanation for this is that these *ortho*-substituents induce a conformational change in the diphenyl ether system which makes binding at the active site less favourable.

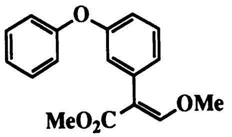
Another consequence of introducing these substituents was that the (octanol/water) log P's were increased by an estimated 0.5 to 0.8 and this (at least in part) led to loss of activity *via* root uptake. Since systemic activity is desirable in a commercial fungicide, we went to some lengths to prepare further analogues with lower partition coefficients.

Introduction of a Ring Nitrogen

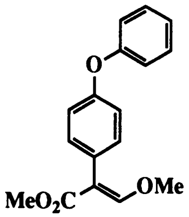
Apart from the introduction of substituents with negative π values, we found that an effective way of lowering the log P in this series was to replace one of the benzene rings of the diphenyl ether with a nitrogen heterocycle. The pyridine **12**, which was prepared according to the steps shown in Figure VII, is an example of such a compound (*8*).

As predicted, the partition coefficient of pyridine **12** (measured log P = 2.6) was significantly lower than the benzene analogue **13** (estimated log P = 4.1) and as a consequence very good levels of systemic activity were achieved (Table I). Later work established that the position of the nitrogen atom in the ring and the nature of the

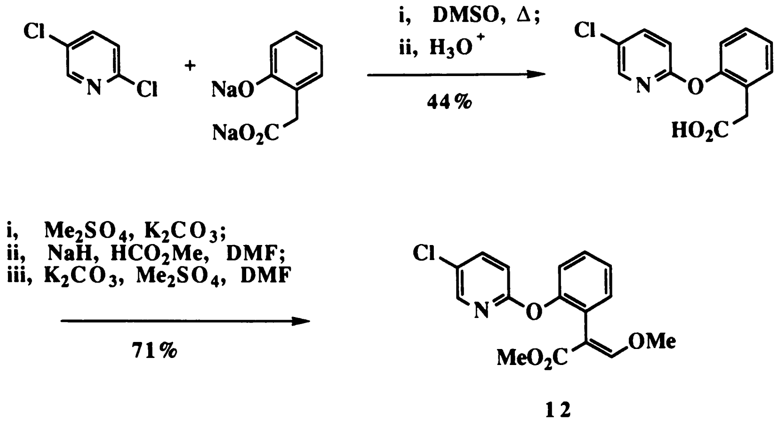
Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034



10



11


Cl
N
Cl
+
NaO
NaO2C
i, DMSO, Δ;
ii, H3O+
44%
Cl
N
O
HO2C
i, Me2SO4, K2CO3;
ii, NaH, HCO2Me, DMF;
iii, K2CO3, Me2SO4, DMF
71%
Cl
N
O
MeO2C
OMe

12

Figure VII : Synthesis of Pyridine 12

substituents have a crucial bearing on the physical and biological properties of compounds of this type. The results of these studies will be published elsewhere.

Conclusions

Synthetic work around the natural products strobilurin A and oudemansin A has led to the discovery of a new class of synthetic fungicides with high levels of activity, a novel mode of action and physical properties which have been optimised for systemicity. The large number of patent applications published by over 10 different companies during the last five years demonstrate the considerable interest in this area of chemistry within the agrochemical industry.

Acknowledgements

We wish to thank our many colleagues at ICI Agrochemicals who have participated in this project and have contributed to its success.

Literature Cited

1. Nevill, D., Nyfeler, R., and Sozzi, D., *Brighton Crop Protect. Conf., Pests and Diseases-1988*, vol. 1, British Crop Protection Council, Thornton Heath, UK, 1988, pp. 65-72.
2. Beautement, K., Clough, J. M., de Fraine, P. J., Godfrey, C. R.A., *Pestic. Sci.*, 1991, *31*, 499.
3. Becker, W. F., von Jagow, G., Anke, T., and Steglich, W., *FEBS Letts.*, 1981, *132*, 329.
4. Beautement, K. and Clough, J.M., *Tet. Letts.*, 1987, *28*, 475.
5. Anke, T., Hecht, H. J., Schramm, G. and Steglich, W., *J. Antibiot.*, 1979, *32*, 1112.
6. EP178,826 (1984, ICI).
7. EP267,734 (1986, ICI).
8. EP242,081 (1986, ICI).

RECEIVED June 29, 1992

Downloaded by CORNELL UNIV on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch034

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

Chapter 35

Total Synthesis of Naturally Occurring 1,2-Dithiolo[4,3-*b*]pyrrolones and Related Compounds

Ian Dell, Christopher R. A. Godfrey, and David J. Wadsworth[1]

ICI Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY, United Kingdom

A new approach to the total synthesis of the structurally related natural products thiolutin, holomycin, aureothricin, isobutyropyrrothin and xenorhabdins I and IV is described. Application of this chemistry to the preparation of synthetic analogues has provided further information on structure-activity relationships which has been used to improve on the fungicidal activity of the natural products.

For many years natural products have provided chemists with a rich source of ideas for the invention of novel effect-chemicals. Indeed, there are now a significant number of important pharmaceutical products and agrochemicals in the market place which have been developed from a consideration of the structure and properties of biologically active natural products. Although some natural products, such as blasticidin S and kasugamycin, have been used commercially as fungicides *per se* (*1*), there are relatively few examples of compounds which have been successfully used as leads for the discovery of synthetic fungicides with optimised physical and biological properties (notable examples are griseofulvin (*2*) and hadacidin (*3*), and more recently pyrrolnitrin (*4*, *5*) and strobilurin A (*6*)).

Nevertheless, the success of this approach in other areas (such as the pyrethroids) combined with the growing need to develop new products to combat resistance, make the exploitation of natural products an attractive option for the fungicide chemist.

---

[1] **Current address: Ciba-Geigy Agro Division, CH—4002 Basel, Switzerland**

0097–6156/92/0504–0384$06.00/0

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

Thiolutin - Scope For Further Work?

Some years ago, as a result of a screening programme, we became interested in the natural product thiolutin **1a** as a potential lead for synthesis. Thiolutin **1a** and its homologue aureothricin **1b**, were isolated from strains of *Streptomyces* over forty years ago, and shown by classical degradation studies to contain the characteristic 1,2-dithiolo[4,3-b]pyrrole (pyrrothine) nucleus (Figure I) (*7*). By 1969, four other closely related metabolites **1c**, **2**, **3a-b** of this class had been discovered (*8-10*) and further structural evidence obtained by both total synthesis (see below) and, in one instance (*10*), X-ray crystallography. More recently, and during the course of our work in this area, a patent was published by the CSIRO in Australia which described the biological activity of five new homologous compounds, the xenorhabdins I-V **1d**, **1e**, **3c**, **3d** and **3e** (*11*). These metabolites were isolated from cultures of *Xenorhabdus* spp. (bacteria symbiotically associated with insect-pathogenic nematodes (*11*)) and shown to have both antimicrobial and insecticidal activity.

The pyrrothine family of antibiotics has shown interesting levels of activity against a wide range of both Gram-positive and Gram-negative bacteria, as well as ameboid parasites and pathogenic fungi (*8*, *9*, *11-15*). In particular, the biological activity of thiolutin **1a**, the most studied member of the series, has been widely reported in the literature (*16*). For example, prior to our interest in the area the fungicidal activity of thiolutin **1a** against black rot and fire blight on apples (*17*), tobacco blue mould (*18*), wilt on tomatoes (*19*), fungal pathogens of orchids (*20*) and as a soil fungicide (*21*) had all been claimed.

However, apart from some semisynthetic work based on pyrrothine itself (derived from thiolutin **1a** by hydrolysis) reported in the patent literature (*13*,*14*), very little structure-activity work has been published in this area. Similarly, very little is known about the mode of action of the pyrrothines, although thiolutin **1a** is thought to act on nucleic acid metabolism at the RNA polymerase step. It is reported to be a potent inhibitor of RNA chain elongation ($I_{50} = 2 \times 10^{-5}M$) and its action is freely reversible (*22*).

Our interest in the pyrrothines began in the early 1980's, when in-house testing of samples of both thiolutin **1a** and holomycin **3a** confirmed their broad-spectrum fungicidal activity. Of particular interest was the observed protectant activity at 25ppm against the commercially important fungal pathogens *Plasmopara viticola* (vine downy mildew) and *Pythium ultimum* (damping off). Despite the significant prior art in this area and the lack of detailed knowledge about the mode of action, we felt that there was still considerable scope for a more detailed examination of the structure-activity relationships, provided that we could come up with a satisfactory synthetic route to analogues. The main objective of this work, therefore, was to devise a versatile total synthesis of thiolutin **1a** and analogues which would enable us to determine the structural requirements for (and hence optimise) fungicidal activity.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

Synthetic Strategy

Several approaches to the total synthesis of the naturally occurring 1,2-dithiolo[4,3-b]pyrrolones have previously been described in the literature (*23-27*). However, it was clear at the outset that none of these was ideal for our purposes. We therefore decided to develop an alternative route which would enable us to prepare a wide range of analogues in sufficient quantities for testing. The strategy that we finally adopted is illustrated in Scheme I.

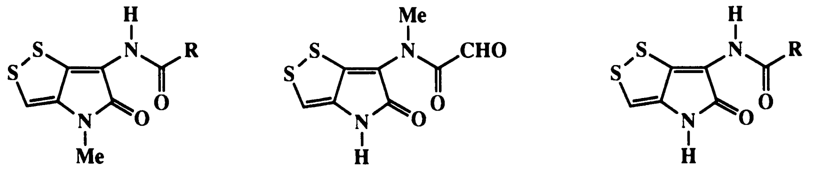
In common with the approach of Hagio and Yoneda (*26*), we chose to close the ring containing the disulfide bond in the final stage of the synthesis by oxidation of the corresponding dithiol **4**. However, the low overall yields quoted in the literature for the preparation of intermediates of type **4** using the *S*-benzyl protecting group, prompted us to examine the *tert*-butyl group as an alternative protecting group for sulfur. The main advantages that this choice offered us were (i) the *tert*-butylsulfide group can be deprotected in high yield and under mild conditions (*28-30*); and (ii) the group could be readily introduced in a nucleophilic sense *via* the commercially available *tert*-butylthiol. This suggested an approach involving the intermediate **5**, which could in theory be derived (*via* the enol **6**) from a symmetrical ketone of type **7**. The application of this chemistry to the synthesis of thiolutin **1a** and analogues is described below.

The Synthesis of Thiolutin 1a

The synthesis of thiolutin **1a** is outlined in Schemes II and III. Treatment of 1,3-dichloroacetone with sodium *tert*-butylthiolate in methanol afforded the symmetrical ketone **8** in 88% yield, together with a small amount of the epoxide **9** (Scheme II). Subsequent reaction with methylamine in the presence of titanium tetrachloride, according to the method of Moretti and Torre (*31*), then led to the formation of the corresponding imine **10**, in equilibrium with its enamino tautomer **11**. Interestingly, later work showed that ammonia itself failed to condense with the ketone **8** under these conditions. The crude mixture of **10** and **11** was then acylated (methyloxalyl chloride - triethylamine) to afford the amide **12** in high yield after recrystallisation. However, attempts to effect ring closure by subsequent treatment of **12** with a base, such as sodium hydride, gave only low yields of the desired product **13**.

Further experimentation revealed that treatment of the mixture of **10** and **11** with a stoichiometric amount of oxalyl chloride in the presence of two equivalents of triethylamine led to the formation of the desired product **13** as a single isomer (tentatively assigned as the *Z*-isomer as shown) in 36% overall yield from the ketone **8**. This reaction, which could be carried out on a large scale, presumably proceeds *via* acylation on nitrogen to give the intermediate **14** followed by intramolecular *C*-acylation.

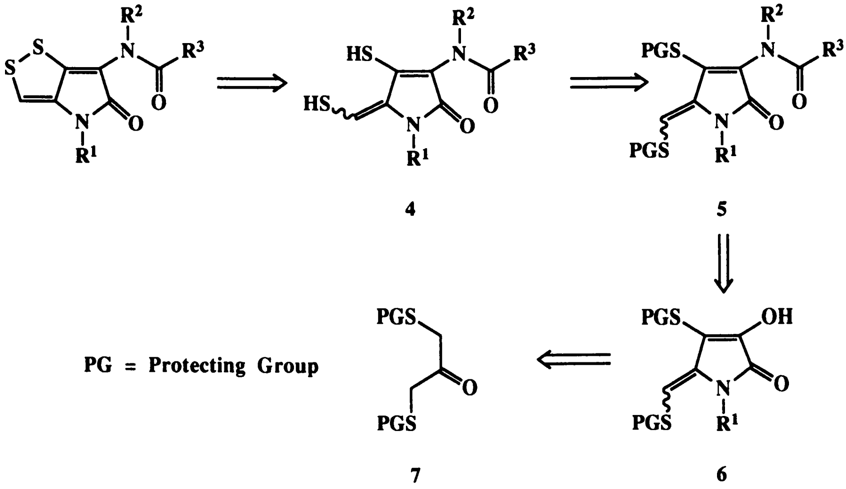
With an efficient route to the intermediate **13** in hand, we next examined the introduction of the second nitrogen atom (Scheme III). Despite the literature precedents for conversion of enols to the corresponding enamines, the reaction proved to be more difficult than expected in this case. The problem was finally overcome by fusing an intimate mixture of **13** and ammonium acetate and heating it for several hours at >200 °C. Under these severe conditions, a mixture of geometric isomers of the corresponding



1 2 VD844 3

a	R =methyl	Thiolutin	a	R =methyl	Holomycin
b	R =ethyl	Aureothricin	b	R =H	VD846
c	R =iso-propyl	Isobutyropyrrothin	c	R =n-pentyl	Xenorhabdin I
d	R =n-pentyl	Xenorhabdin IV	d	R =4-methylpentyl	Xenorhabdin II
e	R =4-methylpentyl	Xenorhabdin V	e	R =n-heptyl	Xenorhabdin III

Figure I : Naturally Occurring 1,2-Dithiolo[4,3-b]pyrrolones

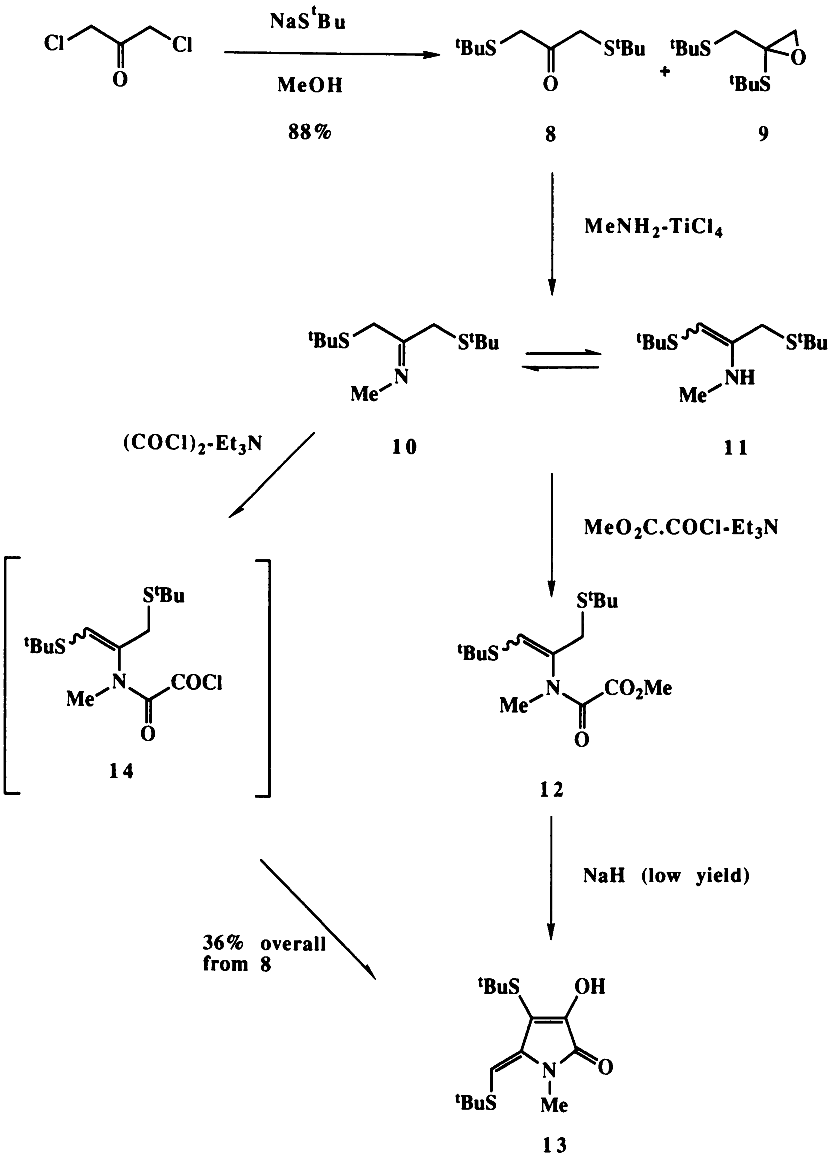


PG = Protecting Group

Scheme I : Synthetic Strategy

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035


NaS^{t}Bu
MeOH
88%
8
9
MeNH$_2$-TiCl$_4$
10
11
(COCl)$_2$-Et$_3$N
14
MeO$_2$C.COCl-Et$_3$N
12
NaH (low yield)
36% overall from 8
13

Scheme II

enamine was produced in very high yield. Subsequent acetylation with acetyl chloride (in the absence of base) afforded the acetamide derivative **15** as an *E,Z*-mixture in essentially quantitative yield.

All that remained at this stage was to deprotect the *tert*-butylthio groups to give the previously described dithiol intermediate **16** and to oxidise it to produce thiolutin **1a**. The method of deprotection chosen was a variant of that reported by Nishimura *et al* (*29*). Thus, treatment of a solution of **15** in trifluoroacetic acid at room temperature with mercury(II) acetate gave the corresponding mercury complex. The solvent was removed by evaporation under reduced pressure and then replaced with DMF. Hydrogen sulfide was bubbled through the resultant mixture to produce a suspension of black mercury sulfide which was filtered off. The filtrate (containing the dithiol intermediate **16**) was finally treated with iodine to give thiolutin **1a** in 57% overall yield from **15** after chromatography.

The overall yield of thiolutin **1a** of 18% from 1,3-dichloroacetone compared very favourably with the existing literature routes. Furthermore, the route seemed ideal for the synthesis of analogues, although the failure of ammonia to react with the symmetrical ketone **8** apparently precluded the preparation of compounds bearing a hydrogen substituent on the ring nitrogen atom of the pyrrothine nucleus. With this in mind we turned our attention to the preparation of further analogues.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

The Synthesis of Analogues

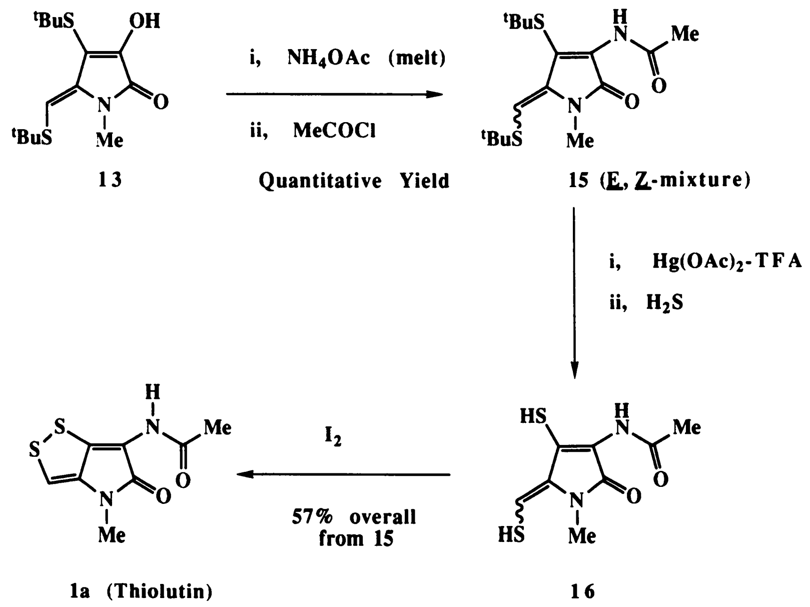
The overall process for the synthesis of further analogues of thiolutin **1a** from ketone **8** is illustrated in Scheme IV. Thus, amination of ketone **8** proceeded well for a wide range of amines R^1NH_2 (with the exception of ammonia itself) to afford the corresponding imine-enamine mixtures **17**, which were immediately treated with oxalyl chloride and triethylamine. A second amination of the resulting enols **18** on heating with an amine acetate $R^2NH_2.HOAc$ under the conditions described above, followed by treatment with an acid chloride R^3COCl, led to the formation of the appropriately substituted intermediates **19** in high yield. Finally deprotection-oxidation gave the desired pyrrothine products **20**.

A wide range of analogues was prepared in this way (see below), including the natural products aureothricin **1b**, isobutyropyrrothin **1c** and xenorhabdin IV **1d**. The yields obtained for the final deprotection-oxidation sequence for these compounds are shown in Table I.

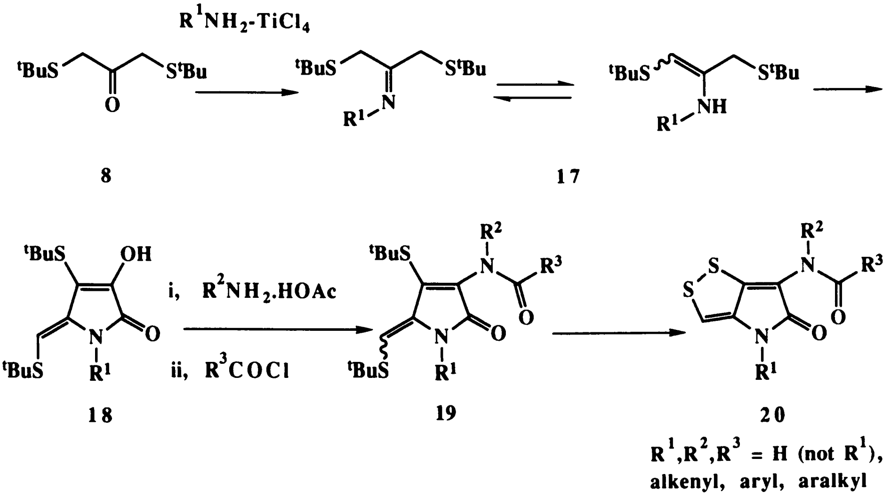
Analogues of Holomycin

Also shown in Table I are yields for the formation of holomycin **3a** and xenorhabdin I **3c**. The breakthrough which allowed the preparation of these compounds (and others bearing a hydrogen substituent on the ring nitrogen of the pyrrothine nucleus) arose in the course of synthesising the *N*-phenyl analogue of thiolutin **1a** (Scheme V). Thus, attempted amination of the enol derivative **21** led to the formation of five products (rather than the usual two *E,Z*-isomers) which were identified as the desired *E,Z*-mixture **22** plus the analogous *N-H* mixture **23** and acetanilide **24**. Prolonged reaction times led to almost complete conversion of **22** to **23** and **24**, presumably *via* nucleophilic attack of ammonia on the ring of **22**, followed

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035


13
i, NH4OAc (melt)
ii, MeCOCl
Quantitative Yield
15 (E, Z-mixture)
i, Hg(OAc)2-TFA
ii, H2S
16
I2
57% overall from 15
1a (Thiolutin)

Scheme III

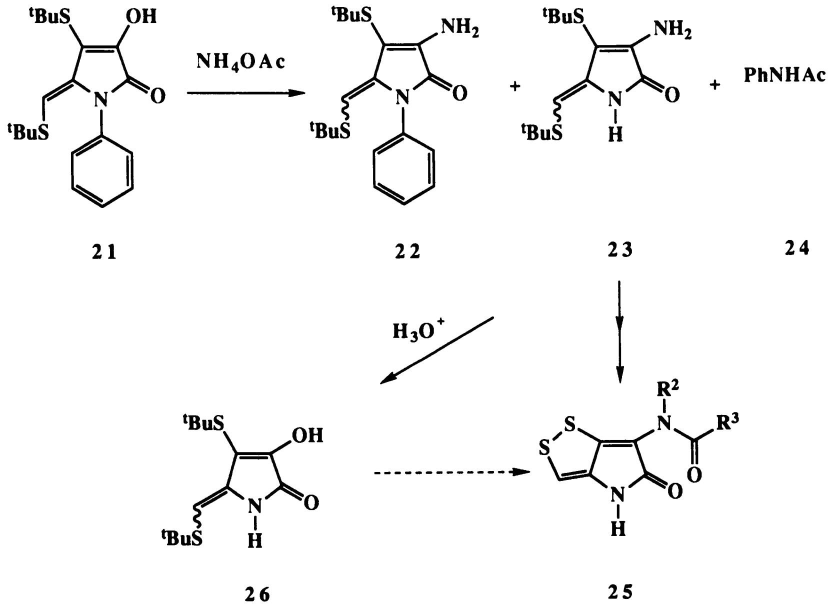

R1NH2-TiCl4
8
17
18
i, R2NH2.HOAc
ii, R3COCl
19
20
R1,R2,R3 = H (not R1), alkenyl, aryl, aralkyl

Scheme IV

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

Table I : Yields Obtained In Deprotection-Oxidation Sequence

	Product (20)	Overall yield after chromatography (%)
1	Thiolutin (1a)	57
2	Aureothricin (1b)	38
3	Isobutyropyrrothin (1c)	36
4	Xenorhabdin IV (1d)	58
5	Holomycin (3a)	50
6	Xenorhabdin I (3c)	28


^tBuS
OH
N
O
^tBuS
21
NH_4OAc
^tBuS
NH_2
N
O
^tBuS
22
+
^tBuS
NH_2
N
O
H
^tBuS
23
+
PhNHAc
24
H_3O^+
^tBuS
OH
N
O
H
^tBuS
26
S
S
R^2
N
R^3
O
N
O
H
25

Scheme V

by expulsion of aniline (which was subsequently acetylated under the reaction conditions). Intermediate **23** was then elaborated to analogues of type **25**, including holomycin **3a** and xenorhabdin I **3c**. Furthermore, mild acidic hydrolysis afforded the enol **26**, which could, at least in theory, be used to prepare compounds bearing additional substitution on the side chain nitrogen (such as the natural product VD844 **2**).

Biological Results

Over 50 analogues of type **20** were prepared in the course this work, representing a wide range of substituents (R^1, R^2, R^3 = H, alkyl, alkenyl, aryl, aralkyl, etc.) attached to the pyrrothine nucleus. Many of these compounds showed fungicidal activity *in vivo* against a broad spectrum of commercially important fungal pathogens (*Plasmopara viticola*, *Phytophthora infestans*, *Cercospora arachidicola*, *Venturia inaequalis*, *Pyricularia oryzae* and *Puccinia recondita*) at concentrations below 100ppm (*32*). Of particular interest was the protectant activity of the best compounds against *Plasmopara viticola* at rates as low as 3ppm. In some cases, *in vitro* fungicidal and antibacterial activity was also observed at 25ppm.

Although significant improvements over the natural product leads were obtained, it was difficult to establish clear structure-activity relationships in the area. Furthermore, all of the synthetic analogues that were tested displayed predominantly protectant activity and little systemicity, which was considered to be an important property for a commercial fungicide. Therefore, in spite of the encouraging levels of activity obtained, the decision was taken to discontinue work in this area.

Conclusions

The approach adopted in this work involved :

(a) The identification of the natural product thiolutin **1a** as a suitable starting point for synthesis as a result of in-house screening against commercially important fungicide targets.

(b) The development of a flexible synthetic route to thiolutin **1a** and related compounds which was capable of producing sufficient quantities of material for screening purposes.

(c) The synthesis of analogues bearing a wide range of substituents in order to study structure-activity relationships and optimise fungicidal and physical chemical properties.

Although significant improvements in activity over the original lead were achieved against several commercially important fungal pathogens (particularly *Plasmopara viticola*), none of the compounds synthesised has been of sufficient interest for further evaluation and our work in this area has now ceased. However, several references to related work have appeared in the recent patent literature (*33-37*).

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

Acknowledgements

We wish to acknowledge the efforts of all of our colleagues at ICI Agrochemicals who have had an involvement or have shown an interest in this work. In particular, our thanks are due to Peter Cleare and his team (large scale synthesis of intermediates), Torquil Fraser (physical chemistry) and Stephen Heaney and Claire Shephard (plant pathology).

Literature Cited

1. Worthington, P. A., *Natural Product Reports*, 1988, 47.
2. Crosse, R., McWilliam, R. and Rhodes, A. J., *Gen. Microbiol.*, 1964, *34*, 51.
3. Dunn, C. L. and Klein, S. P. *Fungicides for Crop Protection*, 1985, 407.
4. Nevill, D., Nyfeler, R. and Sozzi, D., *Brit. Crop Protect. Conf., Pests and Diseases*, 1988, *1*, 65.
5. Gehmann, K., Nyfeler, R., Leadbeater, A. J., Nevill, D. and Sozzi, D., *ibid*, 1990, *2*, 399.
6. Beautement, K., Clough, J. M., De Fraine, P. J. and Godfrey, C. R. A., *Pesticid. Sci.*, 1991, *31(4)*, 499.
7. Celmer, W. D. and Solomons, I. A., *J. Am. Chem. Soc.*, 1955, *77*, 2861, and references therein.
8. Ettlinger, L., Gaumann, E., Hutter, R., Keller-Schierlein, W., Kradolfer, F., Neipp, L., Prelog, V. and Zahner, H., *Helv. Chim. Acta*, 1959, *42*, 563.9. Bahte, D. S., Hulyalkar, K. and Menon, S. K., *Experimentia*, 1960, *16*, 504.
10. Daehne, W., Godtfredson, W. O., Tybring, L. and Schaumburg, K., *J. Antibiot.*, 1969, *22*, 233; Jensen, B., *ibid*, 1969, *22*, 231.
11. *EP126,092* (1984, CSIRO); see also McInerney, B. V., Gregson, R. P., Lacey, M. J.,
    Akhurst, R. J., Lyons, G. R., Rhodes, S. H., Smith, D. R. J., Engelhardt, L. M. and White, A. H., *J. Nat. Prod.*,1991, *54*, 774.
12. Seneca, H., Kane, J. H. and Rockenbach, J., *Antibiotics and Chemotherapy*, 1952, *2*, 357.
13. US Patent 2,689,854 (1954, Pfizer).
14. Brit. Patent 692,066 (1953, Pfizer).
15. Umezawa, H., Maeda, K. and Kosaka, H., *Japan. Med. J.*, 1948, *1*, 512.
16. Breslow, D. S. and Skolnik, H., The Chemistry of Heterocyclic Compounds, Interscience, 1966, Part 1, p417.
17. Murneek, A. E., *Phytopathology*, 1952, *42*, 57.
18. Grosso, J. J., *Plant Disease Reptr.*, 1954, *38*, 333.
19. Gopalkrishnan, K. S. and Jump, J. A., *Phytopathology*, 1952, *42*, 338.
20. Schaffner, C. P., *Am. Orchid Soc. Bull.*,1954, *23*, 798.
21. Zentmyer, G. A., *Phytopathology*, 1955, *45*, 398.
22. Tipper, D. J., *J. Bact.*, 1974, *119*, 795; and references therein.
23. Schmidt, U. and Geiger, F., *Angew. Chem. Int. Ed.*, 1962, *1*, 265; *Annalen*, 1963, *664*, 168.

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

24. Buchi, G., and Lukas, G., *J. Am. Chem. Soc.*, 1963, *85*, 647; *ibid*, 1964, *86*, 5654.
25. Schmidt, U., *Berichte*, 1964, *97*, 1511.
26. Hagio, K. and Yoneda, N., *Bull. Chem. Soc. Japan*, 1974, *47*, 1484.
27. Ellis, J. E., Fried, J. H., Harrison, I. T., Rapp, E., and Ross, C. H., *J. Org. Chem.*, 1977, *42*, 2891.
28. Fujino, M. and Nishimura, O., *J. Chem. Soc. Chem. Commun.*, 1976, 998.
29. Nishimura, O., Kitada, C., and Fujino, M., *Chem. Pharm. Bull.*, 1978, *26*, 1576.
30. Pastuszak, J. J. and Chimiak, A., *J. Org. Chem.*, 1981, *46*, 1868.
31. Moretti, I. and Torre, G., *Synthesis*, 1970, 141.
32. GB2,170,498 (1986, ICI).
33. DE3,434,562 (1986, Boehringer Mannheim).
34. JP63,112,586 (1988, Nippon Kayaku).
35. JP63,284,181 (1988, Nippon Kayaku).
36. J01022-879 (1989, Nippon Kayaku).
37. J02235-885 (1990, Nippon Kayaku).

RECEIVED June 1, 1992

Downloaded by OHIO STATE UNIV LIBRARIES on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch035

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

Chapter 36

Phenylpyrroles, a New Class of Agricultural Fungicides Related to the Natural Antibiotic Pyrrolnitrin

R. Nyfeler and P. Ackermann

Research Services Plant Protection, Agricultural Division, Ciba-Geigy Ltd., 4002 Basel, Switzerland

Pyrrolnitrin, an antifungal secondary metabolite from *Pseudomonas pyrocinia* served as a lead structure for a synthetic optimization program to obtain novel agricultural fungicides. Using the TOSMIC procedure a broad range of structural analogues of pyrrolnitrin were prepared and tested for fungicidal activity. Among the compounds prepared, the 3-cyano-4-phenyl-pyrroles proved to be the most active representatives. CGA 142705, proposed common name fenpiclonil, and CGA 173506 were selected for development, mainly for cereal seed treatment. A broad spectrum of fungicidal activity, good light stability and no adverse toxicological properties characterize these compounds. First studies on the mode of action show it to be different from that of pyrrolnitrin.

Introduction. In modern pest management there is a constant need for new plant protection chemicals. Some of the most important reasons are resistance problems as well as high application rates associated with numerous older compounds. In addition, more stringent regulatory requirements call for new appropriate solutions. A first step in the development of novel active substances is the identification of novel lead structures. Several methods can be used for this purpose. Until now random screening and analogue chemistry were the most successful approaches in the search for novel lead structures. Biorational design, expected to become a powerful tool in the future, has not led to any major agrochemical products. Natural products are a further, widely used source for new lead structures in plant protection. This paper demonstrates the successful development of a novel class of agricultural fungicides, the 3-cyano-4-phenylpyrroles, by using the natural product pyrrolnitrin as a lead structure (Figure 1).

Pyrrolnitrin, a secondary metabolite produced by different *Pseudomonas* species, was first isolated from *Pseudomonas pyrocinia (1)* .

Because of its interesting antifungal activity, pyrrolnitrin was developed as an antimycotic for topical application in human medicine and also served as a lead structure for scientists in the field of pharmaceutical research *(2)*.

0097–6156/92/0504–0395$06.00/0

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

The first use of a pyrrolnitrin analogue in plant protection was described in 1969 in a Japanese patent application *(3)*.

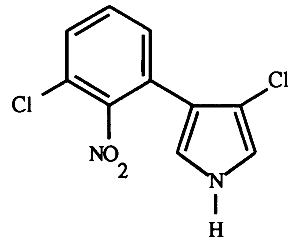
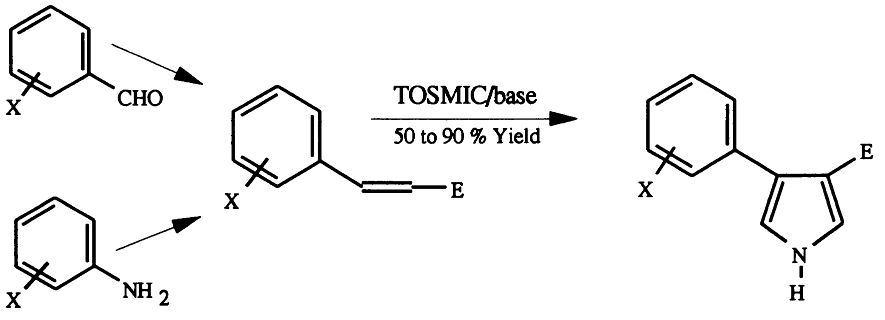


Figure 1 Pyrrolnitrin

In our greenhouse tests, pyrrolnitrin showed interesting activity against a range of phytopathogenic fungi such as *Botrytis cinerea and Pyricularia oryzae.*

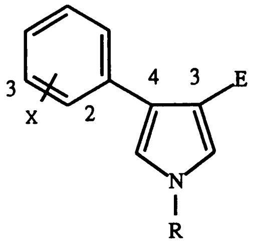
TOSMIC approach for the synthesis of analogues. Despite its apparently simple structure, pyrrolnitrin proved to be a challenge for synthetic chemists. In our opinion, the most useful synthesis was described by Gosteli *(4)*. Starting from 3-chloro-2-nitro-toluene, pyrrolnitrin can be prepared in 6 reaction steps with an overall yield of some 20 %. This approach was not considered attractive for the synthesis of a large number of analogues of pyrrolnitrin. However, a rather simple process to prepare novel pyrroles had been described by van Leusen , using TOSMIC as a key reagent (Figure 2) *(5)*.



E: electron withdrawing groups such as : - NO_2 , - $COOCH_3$, - CN , etc.
X: broad range of different substituents
TOSMIC: p-toluenesulfonyl methylisocyanide

Figure 2 TOSMIC approach

Structure Activity Relations. Using the TOSMIC approach different types of 4-phenylpyrroles were synthesized, and their fungicidal activity was determined against *Botrytis cinerea* on apple in the greenhouse. The influence of the substituents E, X and R, as well as the position of X in structure A (Figure 3), on the fungicidal activity is summarized in Tables I - IV.



A

Figure 3

Variation of the electron withdrawing group E in the 3-position of the pyrrole ring revealed that, among the compounds prepared, the 3-cyanopyrroles showed the highest activity (Table I).

Table I Activity against *B. cinerea* on apple in the greenhouse

EC_{80}: [ppm]	E
>200	$-NO_2$, $-COOCH_3$, $-COCH_3$, $-CONH_2$, $-CON(CH_3)_2$, $-SO_2CH_3$, $-SO_2N(CH_3)_2$, $-P(O)(OCH_3)_2$
20 to 200	$-CSNH_2$
< 20	-CN

Structure A: X = 2-Cl or 3-Cl; R = H

The influence of the substituent X on the fungicidal activity was studied with 3-cyano-4-arylpyrroles. The biological activity of such compounds is determined both by the nature of X and its position in the phenyl ring. To study the influence of the nature of X on the fungicidal activity, the substituents X were chosen in the 2- and 3-positions of the phenyl ring. The results are given in Table II. Based on our experience X has to be an electron withdrawing group such as Cl, Br, CF_3 or $-OCF_2O-$ to reach high fungicidal activity.

Table II Activity against *B. cinerea* on apple in the greenhouse

EC_{80}: [ppm]	X (in 2- or 3-position)
>200	-CN, $-N(CH_3)_2$, $-OCH_3$, $-C{\equiv}CH$, $-OCHF_2$, $-SO_2CH_3$, $-Si(CH_3)_3$
20 to 200	-H, -F, $-CH_3$, $-SCH_3$, $-OCF_3$
< 20	-Cl, -Br, $-CF_3$, $-O-CF_2-O-$

Structure A: E = CN; R = H

To study carefully the influence of the position of X on the fungicidal activity of 3-cyano-4-arylpyrroles, a group of mainly chloro substituted compounds was selected. All compounds, mono- or disubstituted, with a chlorine atom in the 4 position did not show any significant activity in our greenhouse tests. The same is true for disubstituted compounds with chlorine in the 5 position.

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

The 2- and 3-chloro compounds are about equally active in the greenhouse as well as in the field. Highly active fungicides were found with the 2,3-dichloro- and above all with the 2,3(-OCF_2O-) substituted phenyl derivatives (see table III).

Table III Activity against *B. cinerea* on apple in the greenhouse and on grape in the field

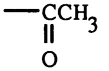
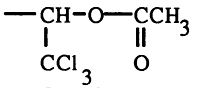
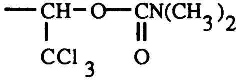
X	Greenhouse EC_{80}: [ppm] [1)]	Field % Control [2)]
2-Cl	10	47
3-Cl	10	49
4-Cl	60	not tested
2,3-Cl_2	6	91
2,4-Cl_2	>200	not tested
2,5-Cl_2	>200	not tested
2,3(-O-CF_2-O-)	0.6	>95

1) apple 2) Riesling x Sylvaner, application rate 75 ai/hl

Structure A: E = CN; R = H

For N-substituted derivatives of the 3-cyano-4-phenylpyrroles, an interesting observation was made (illustrated for the 2,3-dichloro compound in Table IV). Among the derivatives prepared, only those which hydrolysed back to the parent compound rather easily, showed high fungicidal activity. Derivatives which were hydrolytically stable, were either not or only weakly active.

Table IV Influence of hydrolytic stability of N-derivatives on fungicidal activity

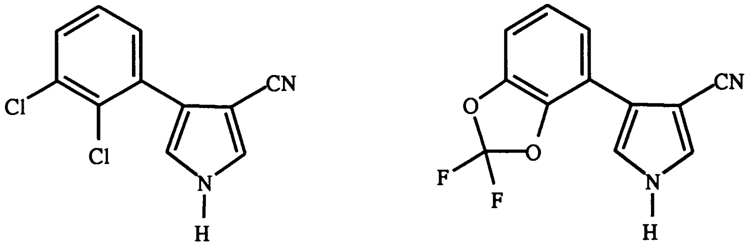
R	Hydrolysis $T1/_2$ 1)	Biol. Activity *Botrytis* /apple
—H	-	high
 $-C(=O)CH_3$	2.8 hrs	high
 $-CH(CCl_3)-O-C(=O)CH_3$	72 hrs	high
 $-CH(CCl_3)-O-C(=O)N(CH_3)_2$	>> 7 d	inactive
$-CH_3$	stable	inactive

1) pH7, 50 ppm in CH_3CN/H_2O (3/7)

Structure A: E = CN, X = 2,3-Cl_2

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

In summary, we found that 3-cyano-4-phenylpyrroles with substituents in either the 2- or the 3-position, and preferably in the 2- and 3-position of the phenyl ring proved to be most interesting. In our hands CGA 142705 and CGA 173506 (Figure 4) showed excellent antifungal activities and therefore they were selected for development.



CGA 142705

4-(2,3-dichlorophenyl)-pyrrole-3-carbonitrile

proposed common name: fenpiclonil

CGA 173506

4-(2,2-difluoro-1,3-benzodioxol-4-yl)pyrrole-3-carbonitrile

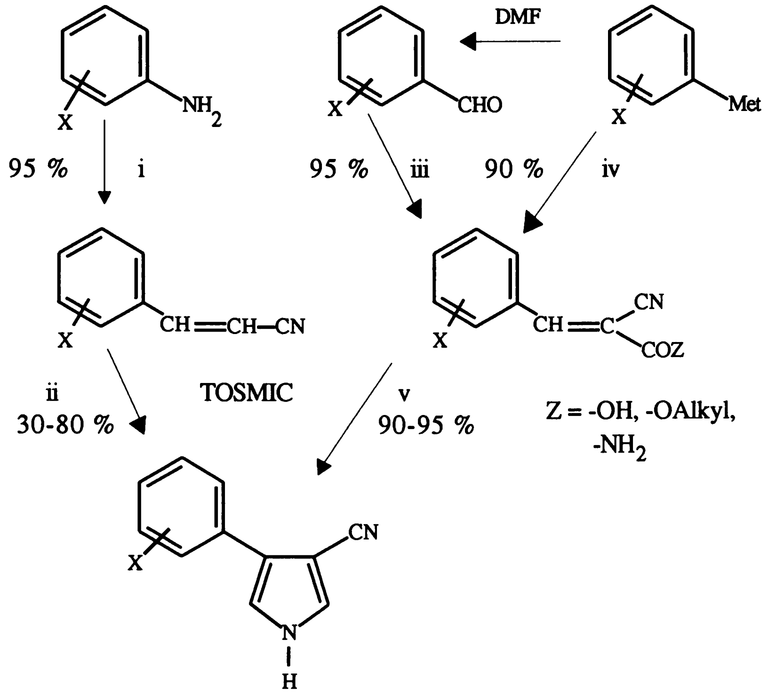
Figure 4 **Most active representatives**

Synthetic Approaches to 3-Cyano-4-Phenylpyrroles. The preparation of 3,4-substituted pyrroles is well documented in the literature. In this paper we will limit ourselves to discuss just two methods, the TOSMIC-route (Figure 5) and an approach which uses α-aminoketones as a key intermediate (Figure 6).

Both methods show four major advantages; they are very flexible and therefore allow the synthesis of many differently substituted pyrroles; they are relatively short; the yields of all reactions involved are good to excellent; and kg-quantities of the most interesting compounds can be prepared easily.

The TOSMIC-route was first described by van Leusen in 1972 *(5)*. Starting from an aniline, the corresponding 3-phenyl-acrylonitrile is prepared by a Meerwein arylation reaction (Figure 5). Treatment of this intermediate with TOSMIC in the presence of a strong base gives the pyrrole derivatives in fair to good yields. More strongly activated double bonds, such as 2-cyano-3-phenylcinnamic acid derivatives can be converted to the pyrroles in excellent yields just using NaOH in aqueous solution *(6)* *(7)*. The required intermediates are easily accessible either by a Knoevenagel condensation of benzaldehydes, or by reacting a metallated phenyl moiety with an ethoxymethylene-cyanacetate derivative *(8)*.

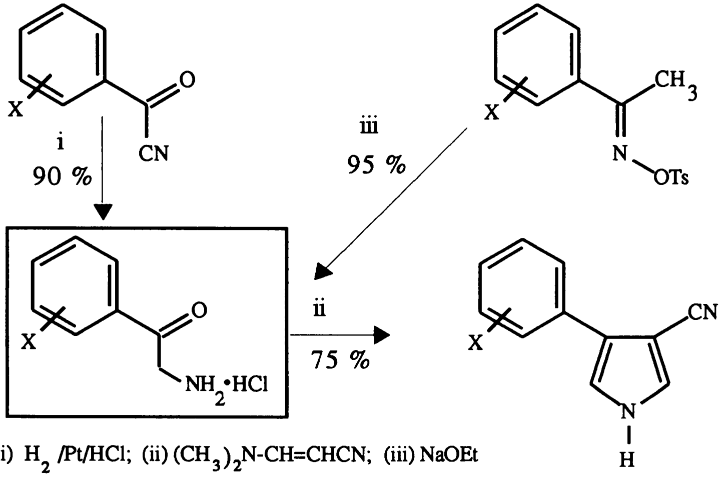
The second synthetic approach to cyanopyrroles is illustrated in Figure 6. The key intermediates, the α-aminoketones are easily prepared in excellent yield either by catalytic hydrogenation of a benzoylnitrile or by base treatment of a ketoxime tosylate, a reaction known as the Neber rearrangement. The α-aminoketones can then be converted into pyrroles in good yield by reacting them with 3-amino-acrylonitriles *(9)*.


X
NH2
95 %
i
X
CHO
DMF
X
Met
95 %
iii
90 %
iv
X
CH═CH—CN
X
CH═C
CN
COZ
ii
30-80 %
TOSMIC
v
90-95 %
Z = -OH, -OAlkyl,
-NH2
X
CN
N
H

(i) a) $NaNO_2$/HCl; b) CH_2=CHCN; c) base; (ii) t-BuOK; (iii) $<\genfrac{}{}{0pt}{}{CN}{COX}$;

(iv) $EtOCH{=}C(CN)CO_2Et$; (v) NaOH.

Figure 5 **TOSMIC-route**


X
O
CN
i
90 %
X
CH3
N
OTs
iii
95 %
X
O
NH2•HCl
ii
75 %
X
CN
N
H

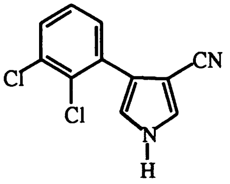
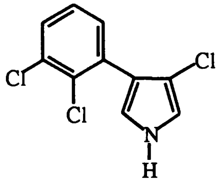
(i) H_2/Pt/HCl; (ii) $(CH_3)_2N$-CH=CHCN; (iii) NaOEt

Figure 6 **α-Aminoketones**

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

Light stability. It has been reported, that pyrrolnitrin is very unstable in light, a property which prevented its practical application in plant protection *(10)*. We have synthesized the chloropyrrole B [Figure 7], a compound very closely related to pyrrolnitrin and compared it with fenpiclonil *(11)*. Using a suntest apparatus (Heraeus) in the laboratory, we found that fenpiclonil has a half-life about a 100 times longer than the chloropyrrole B. In the greenhouse no difference in biological activity was observed. In the field, however, we found 91 % control with fenpiclonil whereas the chloropyrrole was practically inactive. We think that this large difference in biological activity can be explained by the difference in light stability. From these findings it can be postulated, that the 3-cyano group is responsible for the light stability necessary for practical applications.

Compound Test	 fenpiclonil	 B
Light stability $T_{1/2}$ 1)	48 hrs	27 min
Botrytis /apple EC_{80} 2)	6 ppm	6 ppm
Botrytis /grape, percent disease control 3)	91 %	4 %

1) Suntest lamp (Heraeus); Dr. E. Stamm, Ciba-Geigy

2) Laboratory tests, apples stored in boxes in the dark 3) Field tests, Riesling x Sylvaner, 75 g a.i./hl

Figure 7 Light stability of CGA 142705

Toxicological properties of fenpiclonil and CGA 173506. The results from acute toxicity tests with fenpiclonil and CGA 173506 are summarized in Table V. In all the tests conducted, the two compounds showed no adverse effects.

Table V Toxicological properties of fenpiclonil and CGA 173506

Acute toxicity:	fenpiclonil	CGA 173506
LD_{50} oral rat	> 5000 mg/kg	> 5000 mg/kg
dermal rat	> 2000 mg/kg	> 2000 mg/kg
LD_{50} inhalation rat (4h)	> 1500 mg/kg	> 2600 mg/kg
Skin and eye irritation	non irritant and non sensitizer	
Teratogenicity	no teratogenic potential	
Mutagenicity	slight mutagenic effect in vitro. but not in vivo	

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

Biological properties of fenpiclonil and CGA 173506. The biological properties of fenpiclonil and CGA 173506 have been described in detail *(12) (13) (14)* and can be summarised as follows:

Fenpiclonil and CGA 173506 show a similar spectrum of fungitoxic activity. The main strength of both compounds is their activity against cereal seed borne diseases. The level of control that can be achieved with fenpiclonil at a use rate of 20 g active ingredient (ai) /100 kg of seed is shown in Table VI. With CGA 173506 only 5 g ai/100 kg of seed are needed to reach the same level of activity.

Table VI Activity of fenpiclonil as cereal seed treatment

Crop/pathogen	Control at 20 g ai/100 kg seed
Wheat	
Gerlachia nivalis	95 %
Tilletia caries	100 %
Septoria nodorum	60 %*
Rye	
Gerlachia nivalis	90 %
Urocystis occulta	>95 %
Barley	
Gerlachia nivalis	>95 %
Pyrenophora graminea	80 %*
Pyrenophora teres	80 %*

* Activity can be improved by addition of difenoconazol (20 g ai/100 kg seed)

For cereal seed treatment it is particularly important that new active ingredients do not show cross-resistance against MBC-restistant *Fusarium spp.* The phenylpyrrole fungicides meet this requirement and provide excellent control of benomyl resistant strains of *Gerlachia nivalis*. Table VII shows a typical result obtained with fenpiclonil.

Table VII Control of Benomyl resistent strains of *Gerlachia nivalis* on wheat (cultivar Kanzler)

Treatment	% attack
Untreated Check	30 %
Benomyl 113 g ai/100 kg	24 %
Fenpiclonil 20 g ai/ 100 kg	2 %

Both fenpiclonil and CGA 173506 have the potential to control potato diseases caused by *Rhizoctonia solani*, *Helminthosporum solani*, different *Fusarium* *species* , *Phoma exigua* and *Polysculatum pustulans* either as a pre-plant or a pre-storage treatment.

CGA 173506 provides a broad spectrum of activity against foliar pathogens on grape, vegetable, stone fruit and almonds as well as field crops. The major pathogens controlled belong to the genera *Botrytis*, *Monilinia*, *Sclerotinia*, *Rhizoctonia* and *Alternaria*.

In summary, fenpiclonil and CGA 173506 show a broad spectrum of antifungal activity with the main emphasis on cereal seed borne diseases.

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

Mode of action studies. Pyrrolnitrin is known to inhibit the respiratory chain *(15)*. The mode of action of the new cyanopyrrole fungicides however is not yet well understood. First studies were done by Jespers and Davidse *(16)* . They used *Fusarium sulfureum* as the test organism. No inhibition of respiration, chitin-, protein-, DNA- or RNA-synthesis was observed. Fenpiclonil also does not interfere with ergosterol- or lipid biosynthesis. However it caused a fast inhibition of mycelial growth as well as an instantaneous reduction of amino-acid uptake. These latter findings led to the hypothesis that fenpiclonil acts on the cell-membrane. Further studies are needed to define the precise site and mechanism of action. In a recent paper *(17)* Leroux suggests that fenpiclonil has a similar mode of action in fungi as dicarboximides like iprodione and aromatic derivatives such as tolcofos-methyl. However the mode of action of the latter two classes of fungicides is also not yet fully understood. One hypothesis is that they interfere with the cell-membrane *(18)*. It is interesting to note, that the two research groups, using different approaches, came up with similar hypotheses about the mode of action of fenpiclonil.

Summary. Pyrrolnitrin, a secondary metabolite from *Pseudomonas pyrocinia*, shows interesting activity against a number of phytopathogenic fungi. Mainly due to lack of light stability this compound could not be developed as an agrochemical. An optimization program led to the class of 3-cyano-4-phenyl pyrroles, which combine a broad spectrum of fungicidal activity with good light stability. Out of this class of compounds it was possible to select fenpiclonil and CGA 173506 for development. First mode of action studies indicate interference with cell membrane function.

A frequent problem with natural products is their lack of stability towards light or hydrolysis. To our knowledge the above case is one of the few examples where such an instability could be overcome and in addition the biological activity retained or even improved.

Literature Cited

(*1*) Arima,K.; Imanaka, H.; Kousaka, M.; Fukuda, A.: Tamura, G. J. Antibiotics **1965**, *18*, 211 - 219.

(*2*) Suminori, U.; Kazuo, K.; Tanaka, K.; Nakamura, H. Chem. Pharm. Bull. (Tokyo) **1969**, *17*, 559 - 566.

(*3*) Nakanishi, K.; Shimizu, K.; Ouo, K.; Ueda, K. Japanese Patent 50,002,011, **1975** (Appl. 19.3.1969); Chem. Abstr. **1975**, *83*, 38796 r.

(*4*) Gosteli, J. Helv. Chim. Acta **1972**, *55*, 451 - 460.

(*5*) van Leusen, A.M.; Siderius, H.; Hoogenboom, B.E.; van Leusen, D. Tetrahed. Letters **1972**, 5337 - 5340.

(*6*) Geuda, Y.; Muro, H.; Nakayama, K.; Myazki, Y.; Sugita, Y. Ger. Offen DE 3,601,285, 1986.

(*7*) Wollweber, D. Europ. Patent Application 324,336 1988.

(*8*) Schaub, B.; Kaenel, H.R.; Ackermann P. Europ. Patent Application 333,661 1988.

(*9*) Martin P. Europ. Patent Application 174,910 1984.

(*10*) Ueda, A.; Kojima, S.; Yasuda, Y.; Nishikawa, H.; Nakada, A. Europ. Patent Application 19,978 1980.

(*11*) Ueda, A.; Nagasaki, H.; Takakura, Y.; Kojima, S. Europ. Patent Application 92,890 1982.

(*12*) Nevill, D.; Nyfeler, R.; Sozzi, D. Proc. Brighton Crop. Prot. Conf.-Pest. Dis. **1988**, 65.

(*13*) Gehmann, K.; Nyfeler, R.; Leadbeater, A.J.; Nevill, D.; Sozzi, D. Proc. Brighton Crop. Prot. Conf.-Pest. Dis. **1990**, 399.

(*14*) Leadbeater, A.J.; Nevill, D.; Steck, B.; Nordmeyer, D. Proc. Brighton Crop. Prot. Conf.-Pest. Dis. **1990**, 825.

(*15*) Lyr, H. In Antifungal compounds, Siegel, M.R.; Sisler, H.D. Eds. Dekker New York, 1977, Vol. 2, 301 - 332.

(*16*) Jespers, A.B.K.; Davidse, L.C. Abstract of 4th International Mycological Congress, Regensburg, **1990**, 286.

(*17*) Leroux P. Agronomie **1991**, *11*, 115 - 117.

(*18*) Edlich, W.; Lyr, H. In Modern selective fungicides, Lyr, H. Ed. Longman, London 1987, pp 107 - 118.

RECEIVED April 27, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 21, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch036

Chapter 37

Synthesis of Fungicidal Phenylpyrroles

P. C. Knüppel, R. Lantzsch, and D. Wollweber

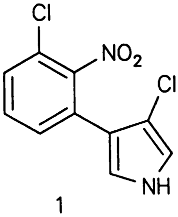
Agrochemical Division, Bayer AG, D–5090 Leverkusen Bayerwerk, Germany

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037

Dedicated to Professor Karl Heinz Büchel on the occasion of his 60th birthday

Pyrrolnitrin was used as a lead structure for new fungicides. Decomposition of members of the phenylpyrrole group was studied; the synthetic derivatives show more stability on exposure to environmental conditions than the natural compound. Fungicidal activities are presented along with some new syntheses.

Pyrrolnitrin is a natural antibiotic which has been isolated from *Pseudomonas pyrrocinia.*



1

Pyrollnitrin
3-chloro-4-(2'-nitro-
3'-chlorophenyl)-pyrrole

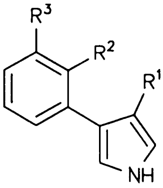
0097–6156/92/0504–0405$06.00/0

A strong inhibition of fungicidal growth is reported *(1)* including fungi associated with the cotton seedling disease complex: *Thielaviopsis basicola, Alternaria* sp. *Verticillium dahliae, Fusarium* sp., and *Pythium ultimum.* If the cotton seeds are treated with pyrrolnitrin and planted in *Rhizoctonia solani* infested soil tubes, there is also a significant increase of surviving seedlings. *(2)*

Decomposition

Because of its photolability the natural compound only shows low fungicidal activities in field trials. Studies on different structural analogues (2) always show a photooxidation of the phenylpyrroles by atmospheric oxygen.

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037



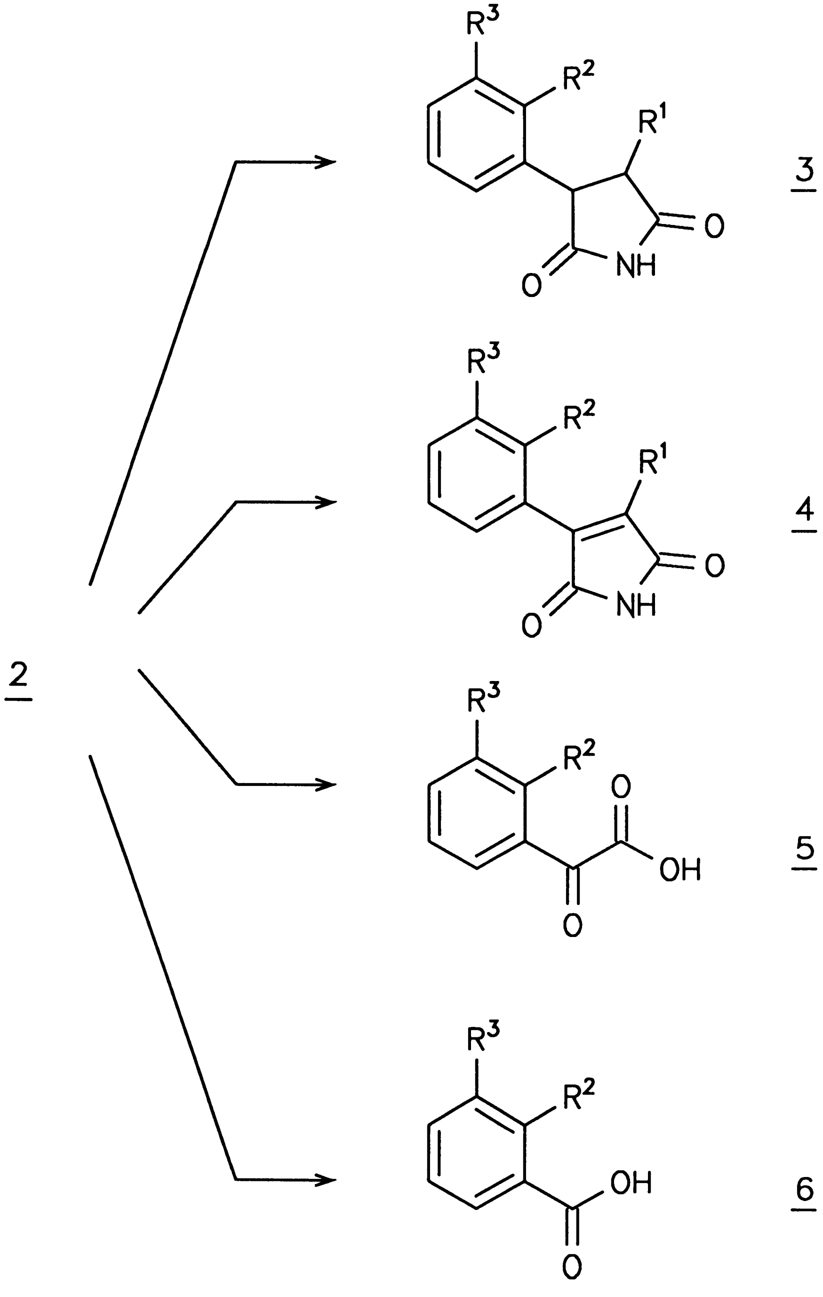
2

R^1 = Cl, CN
R^2, R^3 = Cl, F, CF_3, NO_2

After exposure of the phenylpyrroles to sunlight for 6 hours, the compounds on page 407 were detected and identified by mass spectroscopy.

Variation of the substituents on the phenyl and pyrrole rings can significantly increase the stability. Replacement of Cl and NO_2 on phenyl by F and CF_3, for

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037

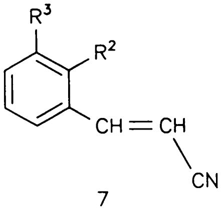

2
R3
R2
R1
O
NH
O
3
R3
R2
R1
O
NH
O
4
R3
R2
O
OH
O
5
R3
R2
OH
O
6

example, and Cl in the pyrrole ring by CN seems to be most favourable. The new derivatives have comparable biological activity in vitro, but the half- lives are increased more than twenty times.(*3*) Good fungicidal activity is now also seen in field trials.

Chemical Synthesis

It was also necessary to find technically relevant syntheses for the phenylpyrroles. The original total synthesis of pyrrolnitrin involved nine steps starting with 2-nitro-3-chlorobenzoic acid.(*4*) Several syntheses have now been developed, starting from readily accessible compounds.

One of the key intermediates is the cinnamonitrile **7**.



7

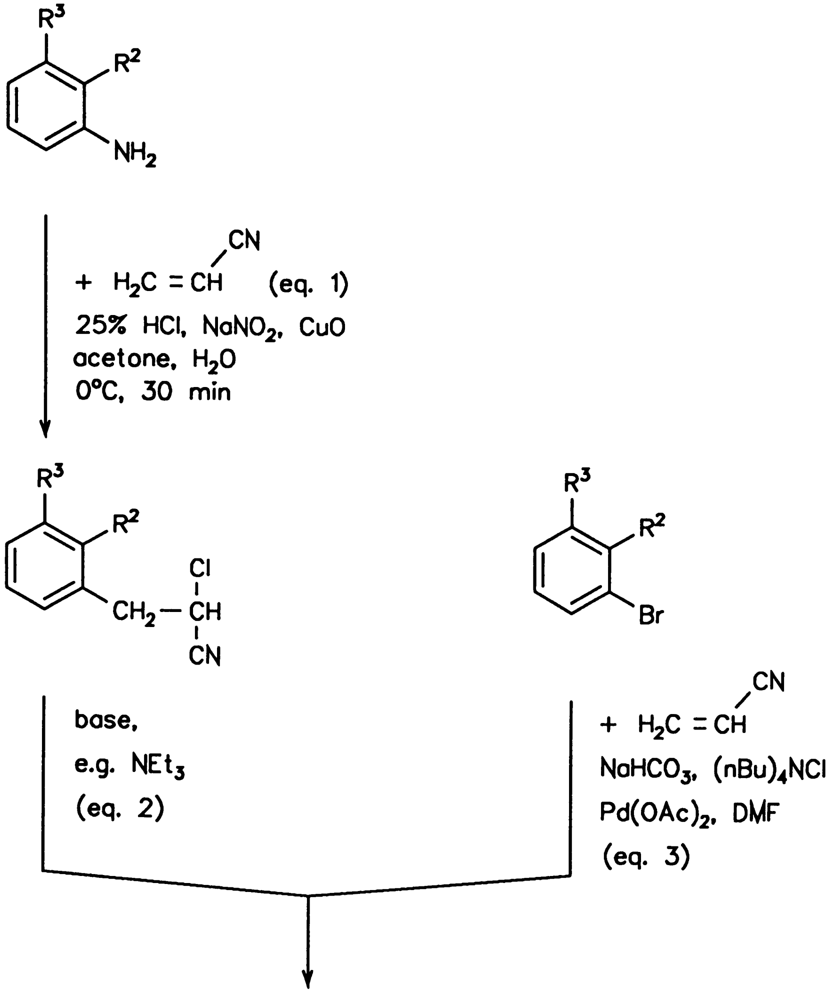
7 can be synthesized from commercially available compounds such as phenyl bromides and anilines.*(5, 6)*

The overall yield for both reactions on page 409 is in the range 85-95%.

It is also possible to start from substituted benzaldehydes, which can be converted to the acrylnitrilo derivatives. (eq.4, (*7*)) The intermediates **7** and **9** can both be cyclised with p-toluenesulfonylmethyl isocyanide.*(6,7)* To get reasonable yields, the reaction with cinnamonitrile **7** needs a stronger base, while the activated **9** forms **10** in one step with simultaneous decarboxylation.

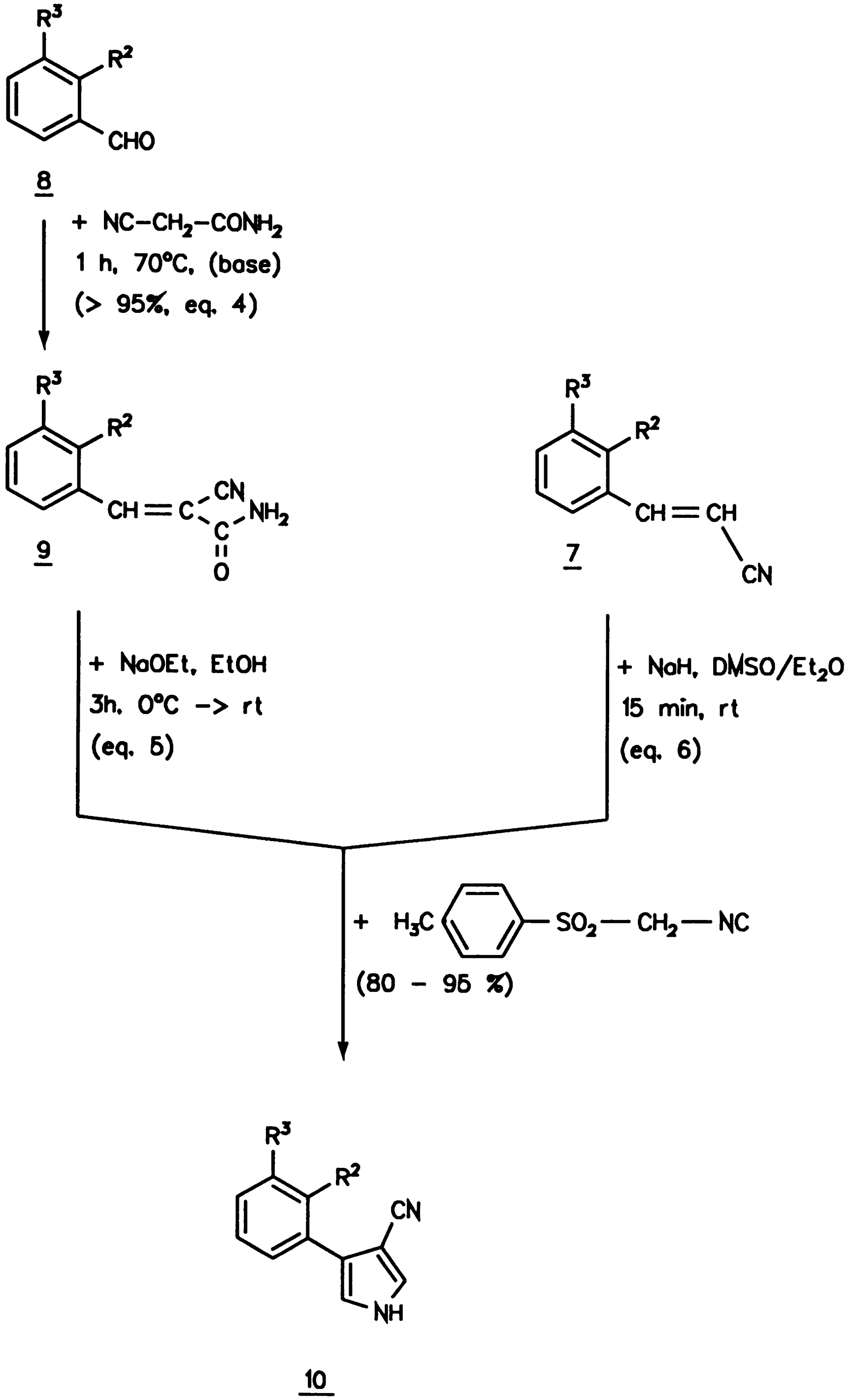
Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037


R3
R2
NH2
+ H2C = CH–CN (eq. 1)
25% HCl, NaNO2, CuO
acetone, H2O
0°C, 30 min
R3
R2
CH2–CH(Cl)–CN
R3
R2
Br
base,
e.g. NEt3
(eq. 2)
+ H2C = CH–CN
NaHCO3, (nBu)4NCl
Pd(OAc)2, DMF
(eq. 3)

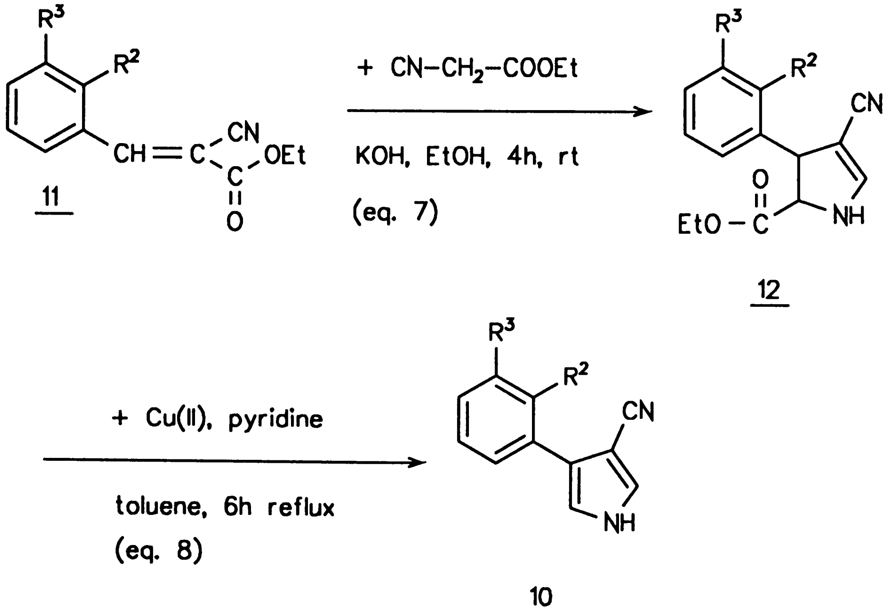
7a R^2 = F, R^3 = CF_3
7b R^2 = F, R^3 = Cl
7c R^2 = CH_3, R^3 = CF_3

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037


R^3
R^2
CHO
8
+ NC–CH$_2$–CONH$_2$
1 h, 70°C, (base)
(> 95%, eq. 4)
CH=C
CN
NH$_2$
C
O
9
CH=CH
CN
7
+ NaOEt, EtOH
3h, 0°C –> rt
(eq. 5)
+ NaH, DMSO/Et$_2$O
15 min, rt
(eq. 6)
+ H$_3$C
SO$_2$— CH$_2$— NC
(80 – 95 %)
NH
10

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037

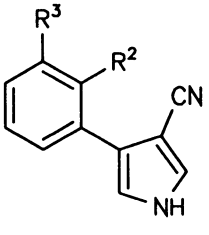
Alternatively, isocyanoacetate can be used as a source of C_2. Reaction with the cyanoacrylate **11** (synthesized analogous to eq. 4) yields the Δ^2-pyrroline-2-carboxylic acid derivative (**12**). In a further reaction step the phenylpyrrole is formed by oxidative decarboxylation.(*8*)


R3
R2
CH=C
CN
OEt
C
O
11
+ CN-CH2-COOEt
KOH, EtOH, 4h, rt
(eq. 7)
R3
R2
CN
O
EtO-C
NH
12
+ Cu(II), pyridine
toluene, 6h reflux
(eq. 8)
R3
R2
CN
NH
10

Biological Activities

The new analogues of pyrrolnitrin show good fungicidal activity against a wide range of fungi including *Pyricularia oryzae*, *Fusarium culmorum* and *Botrytis cinerea*. This can be demonstrated by the MIC values (agar diffusion test) for the pathogens mentioned above (Table 1).

Table 1: MIC values[a]



10 a–c

compound	R^2	R^3	*Pyricularia oryzae*	*Fusarium culmorum*	*Botrytis cinerea*
10a	F	CF_3	32.5	2.1	4.9
10b	F	Cl	5.8	3.7	5.6
10c	CH_3	CF_3	1.2	4.8	1.9

[a] MIC values in ppm, agar diffusion test

Conclusion

Pyrrolnitrin was used to find a new class of fungicidally active compounds. The new fungicides inhibit a wide range of fungi. A rapid decomposition of pyrrolnitrin occurs upon exposure to environmental conditions. The stability can be increased by replacement of Cl with CN on the pyrrole ring and by introducing electron-withdrawing groups, e.g. F, CF_3, as substituents on the phenyl ring. A technically relevant synthesis has been developed starting from readily accessible compounds.

Acknowledgments

We would like to acknowledge the Bayer AG colleagues who have contributed to this work: D. Berg, R. Tiemann (biological data), K. Jelich (synthesis), W. Ockels (MS) and T. Hess (half- life measurements).

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037

Literature cited

1. Arima, K.; Imanaka, H.; Kousaka, M.; Fukuda, A.; Tamura, G. *J. Antibiotics, Ser. A* **1965,** *18*, 201-4
2. Howell, C.R.; Stipanovic, R.D. *Phytopathology* **1979,** *69*, 480-2
3. Knüppel, P.C.; Hess, T.; unpublished results
4. Tanaka, K.; Kariyone, K.; Umio, S.; *Chem. Pharm. Bull.* **1969,** *17*, 622-628 and references therein
5. Wollweber, D.; Brandes, W., European Patent 318704, 1989
6. Knüppel, P.C.; Lantzsch R., to be published
7. Wollweber, D., German Patent 3800387, 1989
8. Wollweber, D., German Patent 3718375, 1988

RECEIVED April 27, 1992

Downloaded by CORNELL UNIV on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch037

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

Chapter 38

Design of Sterol Reductase Inhibitors

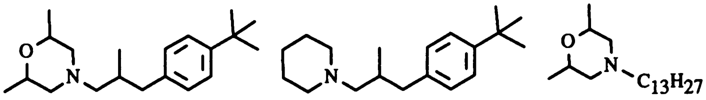
Insights into the Binding Conformation of Tertiary Amine Fungicides

**Gregory S. Basarab, Robert S. Livingston, Steven J. Vollmer,
Curt B. Johnson, and Kevin T. Kranis**

Agricultural Products, E. I. du Pont de Nemours and Company, Stine-Haskell Research Center, Building 300, Newark, DE 19714

The data presented suggest that the binding conformation of tertiary amine fungicides to $\Delta^{8,14}$-sterol reductase in fungi correlates with a *pseudo*-1,3-diequatorial orientation of the amine moiety and a lipophilic group around a cyclopentane. This NADPH dependent enzyme reduces a D-ring sterol double bond through a presumed transition state carbocation which the protonated amine inhibitors are thought to mimic. We designed conformationally restricted tertiary amines based on the sterol D-ring framework and evaluated inhibition of the reductase enzyme in a microsomal assay developed from *Saccharomyces cerevisiae.* Identified was 1-[5-[4-(1,1-dimethylethyl)-phenyl]-1-methyl-6-oxabicyclo[3.1.0]hexan-2-yl]- *cis*-3,5-dimethylpiperidine, [1α,2β,5α] (compound **13a**) as a conformationally restricted tertiary amine that maintains high reductase inhibition.

Inhibition of sterol biosynthesis has emerged as one of the most important strategies to control disease caused by many plant and animal pathogenic fungi. The highly successful azole class of fungicides operates by blocking the 14-demethylase step in the sterol biosynthetic pathway (*1-3*). However, widespread use of such 14-demethylase inhibitors has led to fungal resistance as shown in particular by wheat and barley powdery mildews (*Erysiphe graminis)* with decreased sensitivity to azoles (*3,4*). This resistance problem has led manufacturers and farmers to try to limit its development, either by discontinuing azole use or by mixing and alternating with other mode-of-action fungicides (*5*). As a result, tertiary amine fungicides such as fenpropimorph **1**, fenpropidin **2**, and tridemorph **3** (Figure 1) have gained widespread acceptance and commercial success since they control cereal powdery mildews and slow the development of resistance to azoles. These amine fungicides (also referred to as the morpholine class of fungicides, though fenpropidin does not



1 **2** **3**

Figure 1: Fenpropimorph 1, Fenpropidin 2, Tridemorph 3

0097–6156/92/0504–0414$06.00/0

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

contain a morpholine) operate to varying degrees by blocking two steps downstream from the 14-demethylase step: the $\Delta^{8,14}$-sterol-Δ^{14}-reductase and the Δ^{8}-Δ^{7}-sterol isomerase steps (*6,7*). Akhtar suggested a mechanistic commonality (Figure 2) between the two steps in that protonation of a sterol double bond forms a carbocation transition state which collapses to product by either delivery of hydride from NADPH in the case of the reductase enzyme or removal of one of the 7-position protons in the case of the isomerase enzyme (*8,9*). Hence, that the amine fungicides would inhibit both steps is reasonable. Rahier and Mercer proposed that the amine fungicides block the two steps because of their ability to mimic the carbocation transition state when protonated at physiological pH (*7,10*). Indeed, atom-by-atom mapping of the morpholine of fenpropimorph (or the piperidine of fenpropidin) onto the sterol B-ring and of the *t*-butylphenyl group onto the sterol side chain as diagrammed in Figure 3 provides an intuitively satisfying rationale as to why these potent fungicides operate against the two steps.

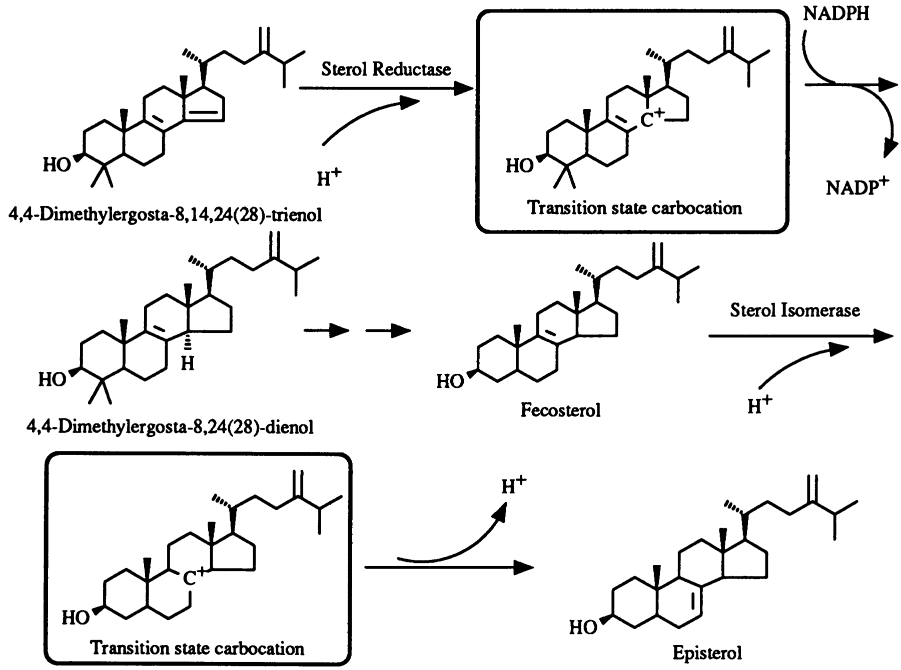
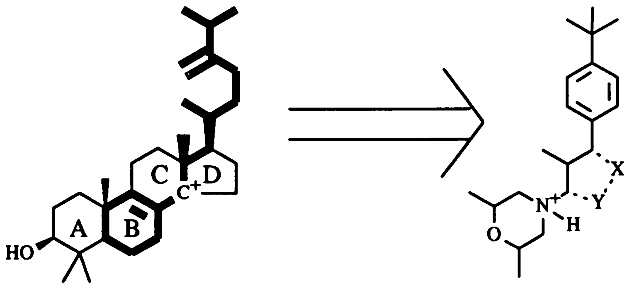

HO
4,4-Dimethylergosta-8,14,24(28)-trienol
Sterol Reductase
H+
HO
C+
Transition state carbocation
NADPH
NADP+
HO
H
4,4-Dimethylergosta-8,24(28)-dienol
HO
Fecosterol
Sterol Isomerase
H+
HO
C+
Transition state carbocation
H+
HO
Episterol

Figure 2: Δ^{14}-Reductase and Δ^{8}-Δ^{7}-Isomerase Transition States

We and others (*11, 12*) reasoned that if fenpropimorph inhibits the reductase and isomerase enzymes by mimicking the sterol carbocations, then restricting the conformationally labile 3-carbon bridge in a five atom ring (X,Y = CH_2-CH_2, Figure 3) would better mimic the sterol D-ring. Such restriction would support the model for inhibition if it afforded potent enzyme inhibitors and would offer an entropic advantage for binding if the inhibitors were preorganized into correct binding conformations. We anticipated that comparing the activities of the diastereomers resulting from such restriction would offer further insight into binding conformations.

Mercer described an assay from *S. cerevisiae* microsomes for sterol Δ^{14}-reductase using [^{14}C]5α-ergosta-8,14,24(28)-trien-3β-ol **4a** as a substrate (*7*). We adapted Mercer's protocols using 4,4-dimethylcholesta-7,14-diene-3β-ol **4b**

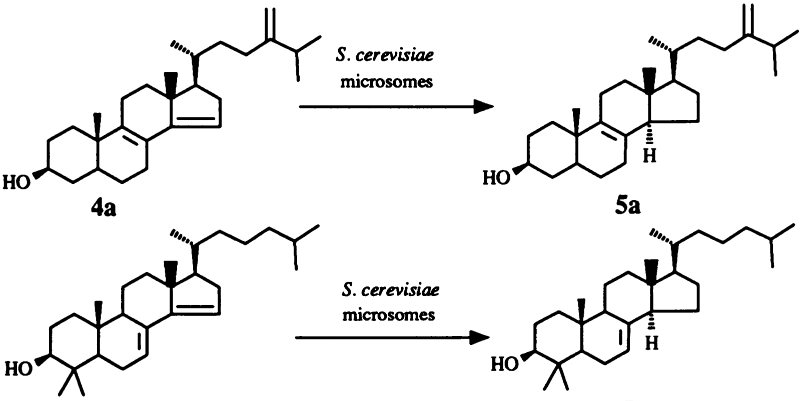


Fenpropimorph: X,Y =H,H

Figure 3: Amines in Relation to Sterol Transition State

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

(Figure 4) as an alternative substrate in our own assay. Gaylor showed that the Δ^{14}-reductase from rat liver microsomes reduced **4b** (*13*); however, the Δ^{14}-reductase from maize failed to reduce the 7,14 diene analogue of **4b** lacking the 4-position methyl groups (*10*). Using **4b** over **4a** as a substrate has the advantage that nascent sterols do not complicate the GC/MS analysis of **4b** and **5b**. Furthermore, since the product **5b** contains the $\Delta^{7\text{-}8}$ olefin as opposed to the $\Delta^{8\text{-}9}$ olefin, complications due to nascent isomerase activity in the microsomal preparation are eliminated. With an assay in hand, we set out to determine the relative ability of conformationally restricted amine fungicides to inhibit the fungal sterol Δ^{14}-reductase.



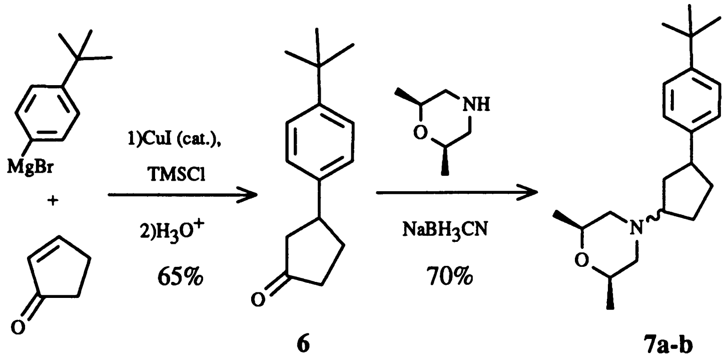
4a 5a 4b 5b

Figure 4: Microsomal Reduction of Sterol Dienes

Chemistry

Synthesis of cyclopentylamines. The synthesis of aryl substituted cyclopentylamines (Figure 5) started with conjugate addition of *t*-butylphenylmagnesium bromide to cyclopentenone. Premixing with trimethylsilyl chloride according to procedures by Johnson (*14*) was required to effect efficient conversion. Reductive amination with *cis*-dimethylmorpholine then gave a 2:1 mixture of *cis* to *trans* products which were separated by chromatography. *Cis*-dimethylmorpholine was chosen for inhibition assays as the *cis* isomer of fenpropimorph has been shown to be more active (*7,15*). The inhibition data presented (*vide infra*) will be compared to the *cis*-dimethylmorpholine diastereomer of fenpropimorph.

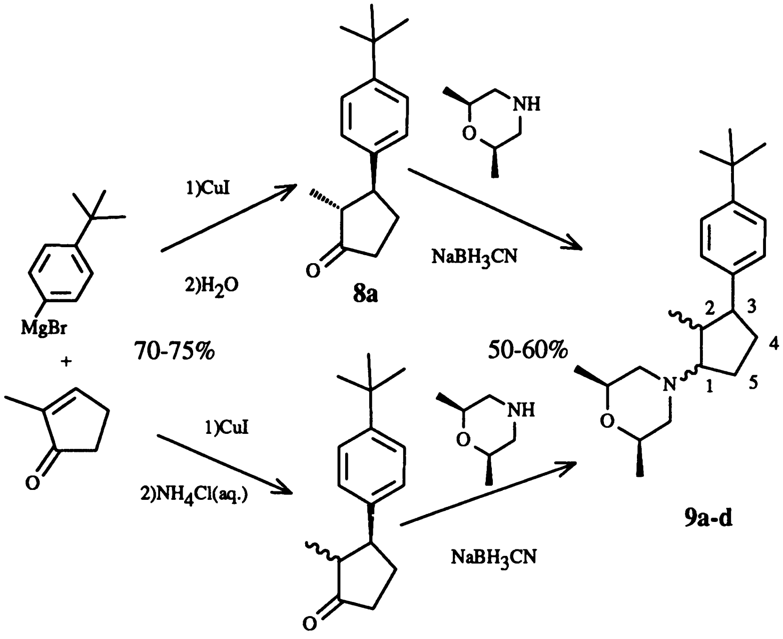
Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038



6 **7a-b**

Figure 5: Synthesis of Cyclopentylamine Diastereomers

The synthesis of methyl substituted cyclopentylamines (to correlate with the methyl substituent on the fenpropimorph bridge) proceeded as above except that trimethylsilyl chloride was not needed for the first conjugate addition step (Figure 6). Quenching the conjugate addition with base or acid afforded only the *trans*-cyclopentanone diastereomer while quenching with excess aqueous ammonium chloride by inverse addition led to a 2:1 mixture of inseparable *cis* to *trans* diastereomers. However, reductive amination of either the pure *trans*-cyclopentanone or of the mixture of *cis*- and *trans*- afforded all 4 possible diastereomers.



(1:1 diastereomeric mixture)

8a + 8b

Figure 6: Synthesis of Methylcyclopentylamine Diastereomers

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

Since there was some isomerization of the *trans*-methyl group to the *cis* orientation, the reductive amination appeared to proceed in part through an enamine intermediate. The diastereomers of **9** were separated by chromatography of the free bases and fractional crystallization of the hydrochloride salts. The relative configuration of the most active diastereomer **9b** (*vide infra)* was shown to have the methyl group *trans* to the phenyl and morpholine rings (C1,C2,C3: *rel-R,R,S*) by X-ray crystallographic analysis of its hydrochloride salt; that of the next most active diastereomer **9a** from X-ray has the all *cis* configuration (*rel-R,S,S*).

As our work was in progress, Urch (*11,16*) published his own work on the synthesis and biological evaluation of cyclic tertiary amines including the diastereomers corresponding to **7** in Figure 5. Though our synthetic schemes parallel his, we looked more closely at separation and characterization of individual diastereomers corresponding to **7** and **9**. Urch claimed that the 2 diastereomers corresponding to **7** were of about equal activity against barley powdery mildew. More recently, Huxley-Tencer (*12*) described work on the synthesis and separation of the 4 optical antipodes corresponding to **7** and showed that highest activity resided in the (1*R*, 3*S*) isomer based on an *in vitro* isomerase assay with *Ustilago maydis* and on control of barley powdery mildew.

Synthesis of oxabicyclo[3.1.0]hexane amines. Since the cyclopentane rings of the amines described thus far are fairly flexible yet are designed to mimic a fairly rigid D-ring of a sterol, we felt that we could impart rigidity by fusion of the cyclopentane with an epoxide. The synthesis of the *trans* epimer of such an epoxycyclopentyl amine was carried out stereoselectively as outlined in Figure 7. Basic hydrogen peroxide oxidation of cyclopentenone **10** (*15)* failed to give any epoxide; however, lithium aluminum hydride reduction of **10** followed by m-CPBA oxidation gave the *cis*-epoxyalcohol **11** as a single diastereomer (greater than 95%) with the hydroxyl group directing epoxidation as is well known (*17*). Pyridinium chlorochromate

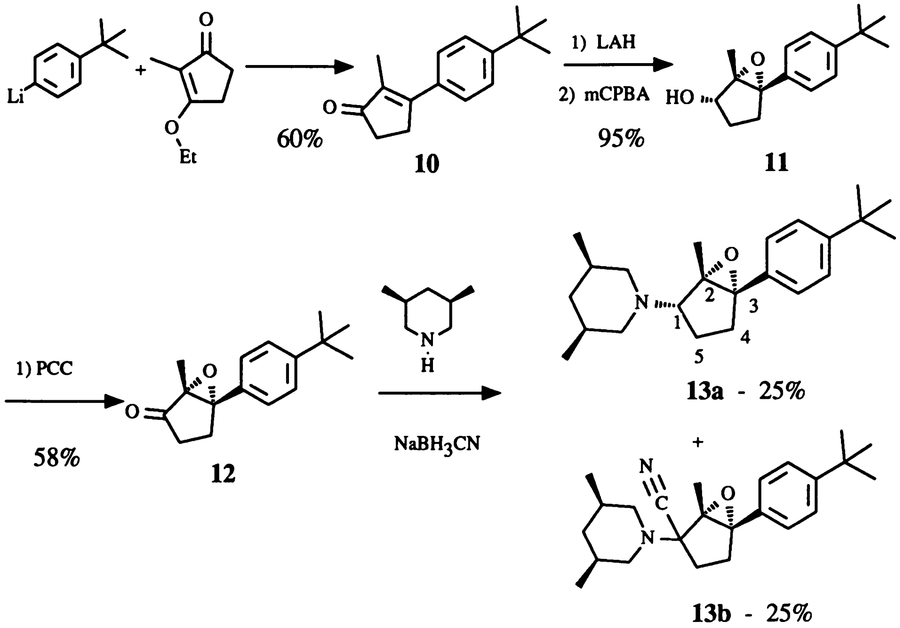
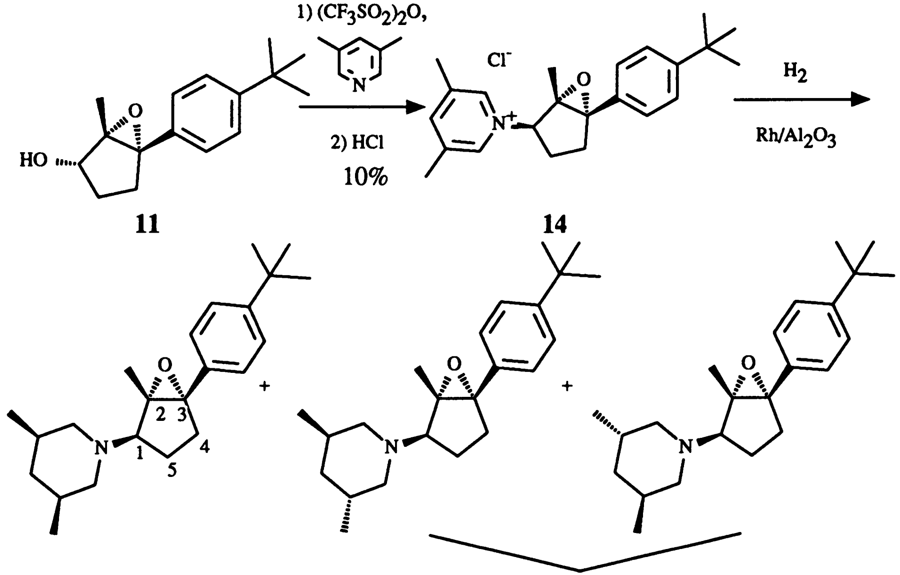


Figure 7: Synthesis of *trans*-Epoxycyclopentylamines

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

oxidation was followed by reductive amination to afford products with the amines *trans* to the phenyl and methyl substituents (*cis* to the epoxide) as in piperidine **13a.** The *cis* epimer was not detected to the limits of analysis by NMR. The Strecker aminonitrile **13b** was generally seen as a by-product of the reductive amination and was assumed to have the piperidine *trans* to the phenyl substituent by analogy. Similar nitrile by-products have been noted by others in moderately hindered systems (*18*). Coupling constants of 10 and 7.6 Hz were seen for the hydrogen on C1 (cyclopentane numbering) of **13a** in the ^1H NMR. A computer model (*19*) of **13a** shows dihedral angles of 151° and 30° for the C1 hydrogen to the vicinal hydrogen atoms at C5 which calculate to coupling constants of 9 and 8 Hz using a Karplus relationship (*20*). To further support the assigned stereochemistry, $NaBH_3CN$ reduction of **12** afforded only **11** (J's = 8, 7 Hz for the C1 proton) within the limits of detection by NMR. The observed stereochemistry of the reductions can be explained either by arguments of product control as the *trans* epimer is undoubtedly less congested than the *cis*, or of steric control as the methyl and phenyl substituents, being in *pseudo*-equatorial orientations, do not block axial hydride attack (*21*). A model of **12** (not shown) suggests that equatorial attack is hindered by the C-5 equatorial hydrogen favoring axial hydride attack and leading to the observed *trans* isomer similar to steric influences for the reduction of cyclohexanones (*21*).

Diastereomers with the piperidine *cis* to the methyl and phenyl substituents were produced by treatment of **11** with trifluomethanesulfonic anhydride in 3,5-lutidine as solvent followed by hydrogenation affording a 3:1 mixture of **15a** and **15b,** the latter an inseparable mixture of diastereomers (Figure 8). The proton at C1 for **15a** and **15b** showed a doublet (J = 7 Hz, versus a doublet of doublets, J's = 8 and 1 Hz as predicted by the Karplus relationship) verifying the assigned stereochemistry. The piperidine methyl groups of the major isomer **15a** were expected to be *cis* in accord with literature reductions of 3,5-lutidine (*22*). The assignment is supported by ^{13}C NMR which shows 6 resonances (the 2 methines being coincident) for the dimethylpiperidine. The ^{13}C NMR of **15b** shows only 4 resonances for



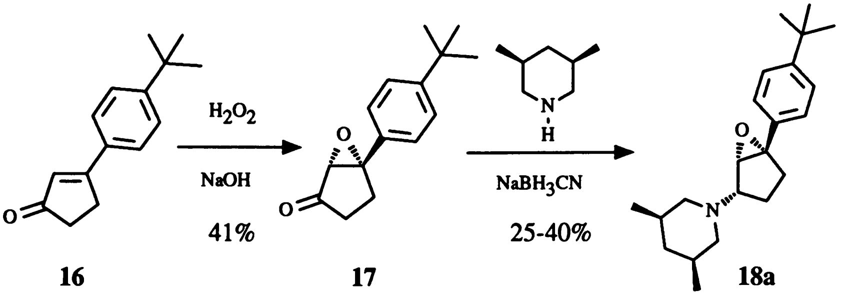
15a - 75% **15b** - 25%

Figure 8: Synthesis of *cis*-Epoxycyclopentylamines

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

the dimethylpiperidine (the chemical shifts due to the diastereomers were otherwise coincident) due to the piperidine C_2-axis of symmetry.

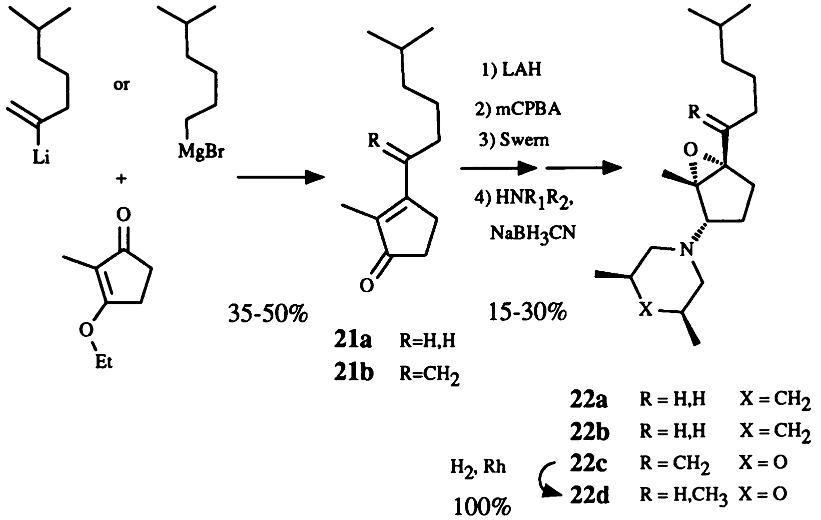
Epoxycyclopentylamines such as **18a** were synthesized by treatment of **16** with basic hydrogen peroxide followed by reductive amination (Figure 9). As before, the reductive amination gave one detectable stereoisomer consistent with the *trans* relationship. Since **17** lacks a methyl group at C-2, the steric control argument for hydride attack holds presumably even more than for **12**. Product development control might suggest that more of the *cis* isomer would have been observed.



16 **17** **18a**

Figure 9: Synthesis of Epoxycyclopentylamines

Since the *t*-butylphenyl groups of the compounds described thus far are thought to mimic aliphatic sterol side chains, inhibitors with such side chains were synthesized. Cyclopentenones **21** were converted to epoxyketones by carbonyl reduction, epoxidation and re-oxidation (Figure 10). In the case of **21b**, reduction of the carbonyl followed by m-CPBA oxidation selectively epoxidized the endocyclic tetrasubstituted olefin over the side chain methylidine. Subsequent Swern oxidation and reductive amination afforded **22c**. Hydrogenation of **22c** afforded a 1:1 mixture of methyl epimers **22d** which proved inseparable in our hands. Not surprisingly, the stereochemical assignments parallel those made for the aromatic analogues.



21a R=H,H
21b R=CH_2

22a R = H,H X = CH_2
22b R = H,H X = CH_2
22c R = CH_2 X = O
22d R = H,CH_3 X = O

Figure 10: Epoxycyclopentylamines with Aliphatic Side Chains

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

Results and discussion

Enzyme assay. The Δ^{14}-reductase assay (*7*) contained 250 µg of microsomal protein prepared from *S. cerevisiae* (strain YPH499), 5.17 µg (12.4 nM) of 4,4-dimethyl-5α-cholesta-7,14-diene-3β-ol **4b** affording a concentration of approximately 2X over K_m, 100 µg of detergent WR1339, 2 mM of NADPH, 0.1 mM EDTA, 10 mM KCN, and 20% glycerol in 100 mM HEPES pH 7.4. Four concentrations of inhibitor in DMSO ranging from 2-2000 ng/ml were used. After 25 minutes at 30°C, saponification with KOH/ethanol was followed by extraction into hexane. The sterols were analyzed by GC with a mass selective detector monitoring the ion range 412 to 416 m/z (substrate **4b** at 412, product **5b** at 414). Variation in recoveries were corrected for by monitoring the internal standard dihydrocholesterol at 288 m/z. An I_{50} value was determined from the dosage/response curve and represents the inhibitor concentration required to reduce conversion of **4** to **5** by 50% of the control. For the purpose of discussion, we referenced the I_{50} values to the I_{50} number of the *cis*-dimethylmorpholine diastereomer of fenpropimorph (I_{50} = 0.065 µM in our assay).

Table I shows the data comparing the inhibition of Δ^{14}-reductase by fenpropimorph **1a** and its *des*-methyl analogue **1b** with the two cyclopentylamine diastereomers **7a** and **7b** and the four methylcyclopentylamine diastereomers **9a-9d**. Rotational restriction by tethering the 3-atom bridge of fenpropimorph in a 5-membered ring still maintains inhibitory activity; however, the relative configuration around the 5-membered ring plays an important role. Thus, placement of the morpholine and phenyl rings 1,3 on a cyclopentane does indeed approximate the active conformation of fenpropimorph. However, the ideal relative orientation on the cyclopentane is perhaps more obscure. The X-ray crystal structures of the hydrochloride salts of **9a** and **9b** were overlaid on an optimized (*19*) structure of the carbocation proposed for the reductase reaction (see Figure 2) by mapping the five carbon atoms of the cyclopentane rings of the inhibitors onto the D-ring of the carbocation (Figures 11 and 12). The D-ring of the carbocation can be characterized as having an envelope pucker (*23*) with C-17 lying below the plane defined by the other D-ring carbon atoms. The crystal structure of **9a** in particular gives qualitatively a satisfying overlay with the carbocation: the phenyl group and the morpholine ring in *pseudo*-equatorial orientations align with the B-ring and side chain of the sterol while the axial methyl substituent aligns with the angular methyl group at the sterol C/D ring fusion. Huxley-Tencer also proposed that the phenyl group and morpholine ring for their most active isomerase inhibitors occupy *pseudo*-equatorial orientations (*12*). The *pseudo*-equatorial orientation is optimal because it allows for a flatter overall shape similar to that of the sterol. The crystal structure of **9b** gives a less satisfying overlay onto the reductase carbocation (Figure 12) in that the morpholine ring occupies a *pseudo*-axial orientation and can not be aligned with the sterol B-ring. Nevertheless, it had proven to be three times more potent of an inhibitor than **9a**. Crystal structures do not represent the only accessible energy minima available to the inhibitors as there exist many other reasonable envelope and half-chair conformations for cyclopentanes (*23*). A conformation that places the phenyl and morpholine ring in *pseudo*-equatorial orientations exists for **9b** (not shown); calculations show it to be 1.5 Kcal lower in energy than the crystal structure conformation (*19*). Because of their flexibility, any of the diastereomers of **9** or **7** could fit to varying degrees into the space defined by the sterol. Indeed, all four diastereomers of **9** are quite active against the reductase enzyme with activity being within an order of magnitude of that of fenpropimorph. As mentioned, Huxley-Tencer (*12*) separated the four enantiomers of **7** and showed them all to be active to varying degrees against barley powdery mildew. They concluded that optimal activity correlates with the *R* absolute configuration at C1. Though our data do not dispute this

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

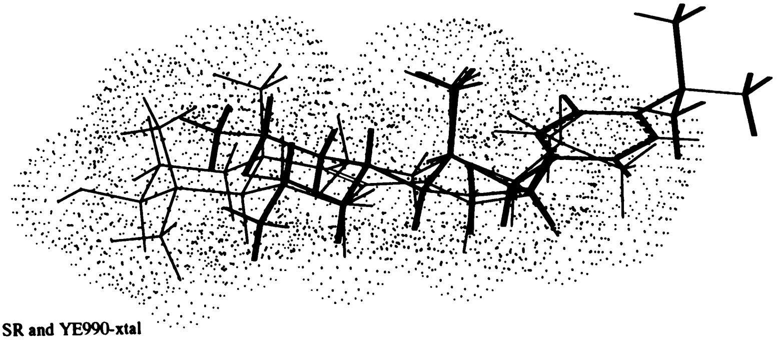


Figure 11: Crystal structure of 9a (HCl salt) Superimposed on the Sterol Reductase Carbocation - The phenyl, methyl and morpholine substituents of 9a (thick wire diagram) are all *cis*. The side chain of the carbocation (thin wire diagram with dot surface) is truncated to an isopropyl group.

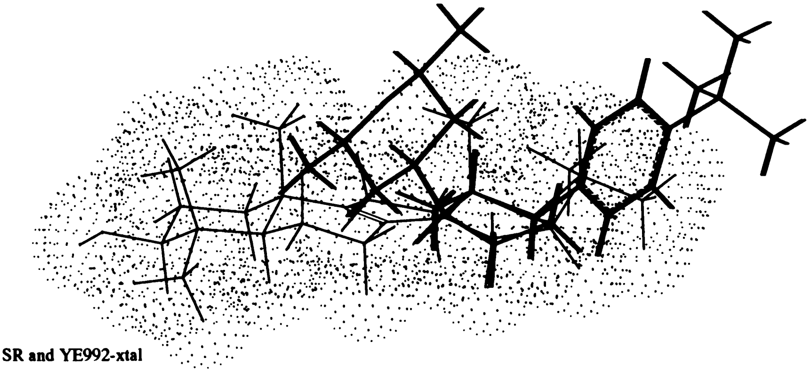
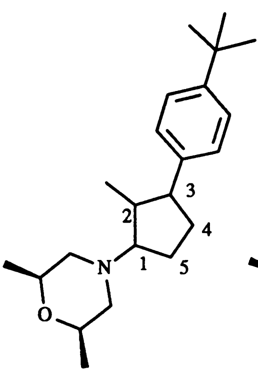
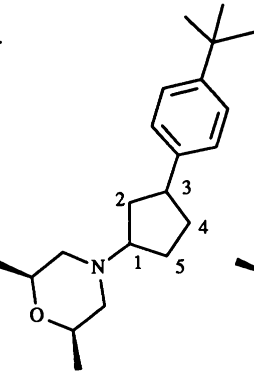


Figure 12: Crystal structure of 9b (HCl salt) Superimposed on the Sterol Reductase Carbocation - The methyl group of 9b (thick wire diagram) is *trans* to the morpholine and phenyl substituents. The side chain of the carbocation (thin wire diagram with dot surface) is truncated to an isopropyl group.

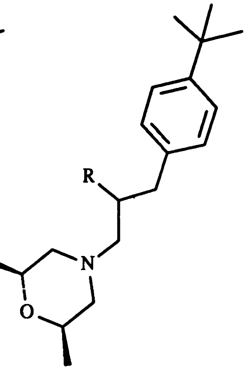
Table I: Reductase Inhibition by Cyclopentylamine Diastereomers



9a-9d



7a,7b



1a R = CH_3 fenpropimorph
1b R = H *des*-methyl fenpropimorph

	Relative Configuration	Sterol Δ^{14}-reductase I_{50}(μM)	Relative Activity (I_{50} Fenpropimorph/I_{50} Inhibitor)
1a	---	0.065	1.0
1b	---	1.4	0.046
7a	(R,S)[a]	0.20	0.32
7b	(S,S)[a]	1.5	0.043
9a	(R,S,S)[b]	0.34	0.19
9b	(R,R,S)[b]	0.10	0.62
9c	(S,S,S)[b]	0.60	0.11
9d	(S,R,S)[b]	0.44	0.14

[a] Based on cyclopentane numbering: (C_1,C_3)
[b] Based on cyclopentane numbering: (C_1,C_2,C_3)

since our compounds are racemic, we propose that the overall geometry that the conformations of the molecule will allow is of greater importance.

The conformationally more rigid compounds with the epoxide fusion are more illustrative of this point. The *trans* isomer **13a** was 40X more potent than the *cis* isomer **15a** as an inhibitor of the reductase enzyme (Table II). Since **13a** has the phenyl and piperidine rings in *pseudo*-equatorial orientations as mentioned earlier, it fits nicely into the space defined by the sterol. However, the cup shape of **15a** with the axial piperidine prevents strong binding to the sterol pocket. Compare the optimized structures of **13a** and **15a** (as conjugate acids) in Figure 13 (*19*).

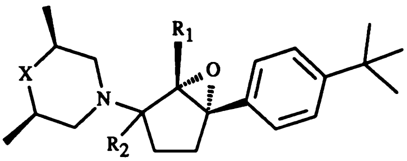
Otherwise, piperidines **13a** and **18a** proved better inhibitors than the corresponding morpholines **13c** and **18b** by an order of magnitude. Activity of **13b** was diminished nearly 50X relative to **13a**. That morpholines are less active than piperidines may be due, in part, to their diminished basicity (typically, pKa ≅ 8 and 10 for morpholines and piperidines, respectively (*24*)). Accordingly, the nitrile of **13b** would lower the basicity of the piperidine (pKa ≅ 4.5, (*24*)), perhaps accounting for diminished activity. It follows that relative basicity would be important to activity since the protonated amines are hypothesized as the inhibitory species.

The compounds with aliphatic side chains in place of *t*-butylphenyl were quite good inhibitors of the reductase enzyme, the best showing 75% the activity of fenpropimorph (Table III). Again, piperidine **22a** was more potent as an inhibitor than morpholine **22b**. More analogues are needed to delineate any side chain structure activity relationships.

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

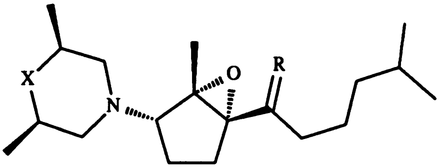
Table II: Reductase Inhibition by Epoxycyclopentylamines



	R_1	R_2	X	Amine Orientation[a]	Sterol Δ^{14}-reductase I_{50}(μM)	Relative Activity (I_{50} Fenpropimorph/I_{50} Inhibitor)
13a	CH_3	H	CH_2	*trans-*	0.026	2.5
13c	CH_3	H	O	*trans-*	0.26	0.25
15a	CH_3	H	CH_2	*cis-*	1.1	0.061
18a	H	H	CH_2	*trans-*	0.23	0.28
18b	H	H	O	*trans-*	4.0	0.016
13b	CH_3	CN	CH_2	*trans-*	1.2	0.053

[a] Relative to the *t*-butylphenyl group

Table III: Reductase Inhibition by Amines with Aliphatic Sidechains



	R	X	Sterol Δ^{14}-reductase I_{50}(μM)	Relative Activity (I_{50} Fenpropimorph/I_{50} Inhibitor)
22a	H,H	CH_2	0.085	0.76
22b	H,H	O	0.32	0.20
22c	CH_2	O	0.33	0.20
22d	H,CH_3	O	0.24	0.27

Whole plant assay. Table IV summarizes the activities of the inhibitors described herein versus powdery mildew on wheat (*E. graminis* f. sp. *tritici*), the protocols for the assay described elsewhere (*25*). The whole plant data correlates to the reductase inhibition for the most part within a series of analogous compounds. Within the more rigid bicyclic series, for example, the activity of **13a** was higher than **13c** which was, in turn, much higher than **15a** and **13b** in both *in vitro* and *in vivo* assays. However, though all the diastereomers of **9** were effective inhibitors and controlled plant disease, the relative activities between the sets of data did not correlate well. Compounds **22a-d** with the aliphatic side chains were moderate to poor fungicides though they were quite active at the enzyme level. Compounds **1b** and **7b**, less active versus the enzyme, showed better fungicidal activity. Finally, though **13a** is not only the best inhibitor of the reductase enzyme and one of the better fungicides in initial plant assays, more stringent advanced greenhouse assays showed it to be 2-4X less active than fenpropimorph against wheat powdery mildew.

Table IV: Activity of Inhibitors Against Wheat Powdery Mildew

Compound	ED_{90}[a]	Compound	ED_{90}	Compound	ED_{90}
1a	20	**9c**	50	**18a**	400
1b	50	**9d**	20	**18b**	400
7a	20	**13a**	20	**22a**	200
7b	20	**13b**	>500	**22b**	200
9a	20	**13c**	100	**22c**	400
9b	20	**15a**	>500	**22d**	200

[a] ED_{90} values in ppm are the concectrations of inhibitor required to give 90% control of the pathogen.

Urch (*11*) reported from plant assays against barley powdery mildew that **7a** and **7b** were both approximately an order of magnitude less active than fenpropimorph. Huxley-Tencer (*12*) reported **7a** to be about an order of magnitude more active and **7b** about equal in activity to fenpropimorph. Different experimental protocols, pathogens and host plants make correlations with our own data difficult to assess.

There are a number of reasons why relative activities would differ between *in vitro* assay and whole plant assays. Most obvious is that Δ^{14}-reductase inhibition is only 1 of 2 mechanisms that fenpropimorph is known to interfere with in the sterol biosynthetic pathway; the relative importance of blocking the reductase step versus the isomerase step for overall fungicidal activity is not clear. Additionally, variation in whole plant activity among compounds could be due to differences between the yeast and powdery mildew reductase enzymes. Unfortunately, the lack of a method to culture powdery mildews limits our ability to carry out biochemical investigations. Finally, the interaction of the inhibitors with the plant are not accounted for by *in vitro* assays. Translocation or metabolism by the plant or fungus play important roles in defining overall activity. Khalil and Mercer recently showed that fenpropimorph affects the sterol content of the wheat plant (*26*), which may be pertinent to phytotoxicity and pathogen control.

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

Summary

Compound **13a** was identified as the best inhibitor of Δ^{14}-reductase from yeast being about 2.5X more potent than fenpropimorph. Figure 14 shows that a model of **13a** overlays well onto the proposed transition state carbocation for the enzyme when mapping the cyclopentane carbons onto the sterol D-ring (*19*). Though the envelope pucker of **13a** differs from that of the sterol D-ring in that the C-5 methylene (cyclopentane numbering) of **13a** lies slightly above the plane of the remaining four carbons, the overall linear shape of the molecule fits well into the sterol space. This is particularly significant since the cyclopentane ring of **13a** is quite conformationally rigid. The epimeric **15a** is locked into a conformation that does not fit well into the sterol space and is thus less active. Hence, the relative configuration of the epoxycyclopentylamines are crucial to determining enzyme activity. Such is not the case with the more flexible cyclopentylamines **7a-b** and **9a-d** since they are more able to adopt reasonable binding conformations. We suggest, therefore, that the active conformation of better reductase inhibitors corresponds to the position of equatorial phenyl and piperidine (or morpholine) rings at the 1 and 3 positions on a puckered cyclopentane.

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

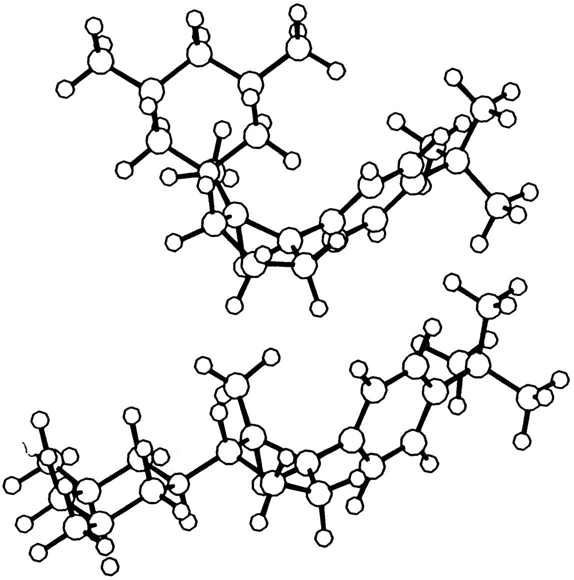


Figure 13: AM1 Optimized Structures of 15a (top) and 13a (bottom).

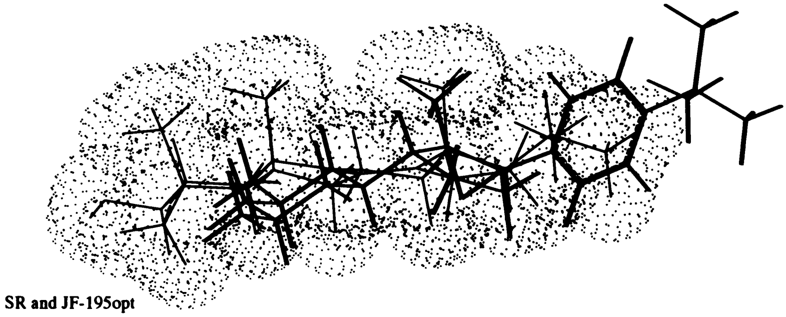


Figure 14: AM1 Optimized Structure of 13a (Conjugate Acid) Superimposed on the Sterol Reductase Carbocation - The morpholine of 13a (thick wire diagram) is *trans* to the methyl and phenyl substituents. The side chain of the carbocation (thin wire diagram with dot surface) is truncated to an isopropyl group.

Downloaded by CORNELL UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch038

Acknowledgments

We are indebted to Louis F. Lardear, William J. Marshall and Joseph C. Calabrese for the X-ray crystal structure determinations, to William Payne for the NMR elucidation of the cyclopentylamine diastereomers, to Martin T. Scott for the purification of sterol substrates, and to Daniel A. Kleier for useful discussions. Plant disease control assays were carried out by Du Pont's Plant Disease Control group.

Literature Cited

1. Kato, T.; Kawase, Y. *Agr. Biol. Chem.* **1976**, *40*, 2379.
2. Kato, T. In *Chemistry of Plant Protection*; Haug, G. and Hoffman, H., Eds., Springer-Verlag, Berlin, 1986, pp. 1-24.
3. Köller, W. In *Fungicide Resistance in North America*; Delp, C.J., Ed., APS Press, St. Paul, Minnesota, 1988, pp. 79-88.
4. Heaney, S.P. *ibid.*, pp 89-92.
5. Scheinpflug, H. *ibid.*, pp 93-94.
6. Baloch, R.I.; Mercer, E.I.; Wiggins, T.E.; Baldwin, B.C. *Phytochemistry* **1984**, *23*(10), 2219-2226.
7. Baloch, R.I.; Mercer, E.I. *Phytochemistry* **1987**, *26*(3), 663-668.
8. Wilton, D.C.; Muday, K.A.; Skinner, J.J.M.; Akhtar, M. *Biochem. J.* **1969**, *114*, 71.
9. Wilton, D.C.; Muday, K.A.; Skinner, J.J.M.; Akhtar, M. *Biochem. J.* **1968**, *106*, 803-810.
10. Taton, M.; Benveniste, P.; Rahier A., *Eur. J. Biochem.* **1989**, *185*, 605-614.
11. Urch, C.J. In *Synthesis and Chemistry of Agrochemicals II*; Baker, D.R., Fenyes, J.G., Moberg, W.K., Eds.; ACS Symposium Series No. 443; American Chemical Society: Washington, D.C., 1991, pp 515-526.
12. Huxler-Tencer, E.F.; Bladocha-Moreau, M. *Pestic. Sci.* **1992**, *34*, 65-74.
13. Paik, Y-K.; Trzaskos, J.M.; Shafiee, A.; Gaylor, J.L. *J. Biol. Chem.* **1984**, *259*(21), 13413-13423.
14. Johnson, C.R.; Moren, T.J. *Tetrahedron Lett.* **1987**, *28*(1), 27-30.
15. Himmele, W.; Pommer, E-H. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 184-189.
16. Anthony, W.M.; Urch, C.J.; Elliot, A.C., EP-B Patent 259977, 1986.
17. Kočovsky, P. *Tetrahedron Lett.* **1988**, *29*(30). 2475-2478.
18. Barney, C.L.; Huber, E.W.; McCarthy, J.R. *Tetrahedron Lett.* **1990**, *31*(39), 5547.
19. Full geometry optimizations were perfomed on a Silicon Graphics IRIS 4d/320 computer, using the semiempirical MOPAC program. The AM1 parameterization was employed for all calculations.
20. Haasnoot, C.A.G., De Leeuw, F.A.A.M., Altona, C. *Tetrahedron* **1980**, *36*, 2783.
21. Richer, J-C. *J. Org. Chem.* **1965**, *30*, 324.
22. Schubart, R.; Ziemann, H.; Wendisch, D. *Synthesis* **1973**, *4*, 220-221.
23. Saebo, S.; Cordell, F.R.; Boggs, J.E. *J. Mol. Struct.* **1983**, *104*, 221-32.
24. Albert, A. In *Physical Methods in Heterocyclic Chemistry, Vol. I*; Katritzky, A.R., Ed.; Academic Press, New York, **1963**, p 63.
25. Basarab, G.S. WO 9204344, 1992.
26. Khalil, A.; Mercer, E.I. *J. Agric. Food Chem.* **1991**, *39*, 404-407.

RECEIVED June 29, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

Chapter 39

Mechanism of the Antifungal Action of (*S*)-2-Amino-4-oxo-5-hydroxypentanoic Acid, RI–331

Inhibition of Homoserine Dehydrogenase in *Saccharomyces cerevisiae*

H. Yamaki, M. Yamaguchi, and H. Yamaguchi[1]

**Institute of Applied Microbiology, University of Tokyo, 1–1–1 Yayoi,
Bunkyo-ku, 113 Tokyo, Japan**

An antifungal amino acid antibiotic, (S) 2-amino-4-oxo-5-hydroxypentanoic acid (RI-331) preferentially inhibited protein biosynthesis in Saccharomyces cerevisiae, by inhibiting biosynthesis of the aspartate family of amino acids (methionine, isoleucine and threonine). This inhibition was effected by impeding the biosynthesis of their common intermediate precursor homoserine. The target enzyme of RI-331 was homoserine dehydrogenase (EC.1.1.1.3). Since such enzyme activity is not present in animal cells, the selective antifungal activity of the antibiotic is thus explained. The antibiotic was active against some plant pathogenic fungi, suggesting the possibility that the antibiotic is useful as antifungal agrochemicals.

In our program seaching for new antifungal antibiotics, we isolated an antifungal amino acid antibiotic, (S) 2-amino-4-oxo-5-hydroxypentanoic acid coded as RI-331 (Fig. 1) from culture broth of Streptomyces sp. The antibiotic has an inhibitory effect against a wide range of yeasts including several pathogenic fungi of medical importance such as Candida albicans and Cryptococcus neoformans. Also the antibiotic was effective in treating murine systemic candidiasis being highly tolerated by experimental animals when given orally or intravenously

---

[1] **Current address: Research Center for Medical Mycology, Teikyo University, 359 Otsuka, Hachioji City, Tokyo 192–03, Japan**

0097–6156/92/0504–0428$06.00/0

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

(1) (Fig. 2). The antibiotic therefore is likely promising for use against systemic cadidiasis in humans. We also described here the inhibitory action of the antibitotic against plant pathogenic fungi.
Our major concern was to understand the biochemical basis of the antifungal action of the antibiotic. In an attempt to clarify the selective antifungal action, we explored the mechanism of action of RI-331 using a susceptible strain of Saccharomyces cerevisiae as an organism tested.

Preferential Inhibition of Protein Biosynthesis by RI-331

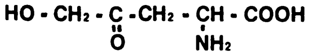
First we studied the effect of the antibiotic on biosyntheses of DNA, RNA and protein by growing yeast cells. The antibiotic preferentially inhibited protein biosynthesis, whereas RNA and DNA biosythses were less susceptible to RI-331 (Table I).

Table I. Effect of RI-331 on Incorporation of Radiolabeled Precursors into Protein, RNA and DNA in Growing Saccharomyces cerevisiae

RI-331 (µg/ml)	[^{14}C] Asn	[^{14}C] Gln
0	17,264 (100)	16,773 (100)
15	5,796 (34)	5,282 (32)
150	1,407 (8)	1,032 (6)

RI-331 (µg/ml)	[^{3}H] adenine taken up into	
	RNA	DNA
0	10,457 (100)	3,543 (100)
15	9,775 (93)	2,930 (83)
150	7,014 (67)	1,956 (55)

SOURCE: Reproduced with permission from ref. 2. Copyright 1990.
The data represent the incorporated radioactivity (dpm). Valuues in bracket represent incorporation as a percentage of the untreated control.



$HO-CH_2-\underset{O}{\underset{\|}{C}}-CH_2-\underset{NH_2}{\underset{|}{CH}}-COOH$

Figure 1. Chemical structure of RI-331

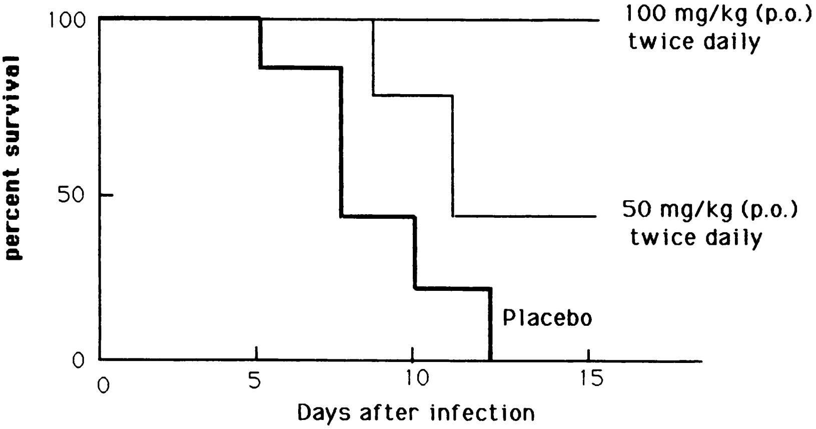


Figure 2. Therapeutic efficacy of oral treatment regimens of RI-331 in mice candidiasis. (Adapted from ref. 1).

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

The protein synthsis in a cell-free system prepared from the yeast cells was however refractory to the antibiotic. These results led us to the possibility that RI-331 acts not on the steps of amino acid polymerization on ribosomes, but blocks de novo biosynthesis of certain amino acid(s). This possibility was checked by analyzing the composition of intracellular amino acids of the yeast treated with RI-331.

Inhibition of Biosynthesis of the Aspartate Family of Amino Acids. In RI-331 treated cells, the pool size of threonine, methionine and isoleucine were markedly reduced (Table II).

Table II. Changes in the Composition of Amino Acid Pools Induced by RI-331 in Saccharomyces cerevisiae

Amino acid	Control (C)	+ RI-331 (R)	R/C
Gly	1.499	1.139	0.76
Ala	5.665	12.237	2.16
Val	1.153	12.949	11.23
Leu	0.207	0.597	2.88
Ile	0.315	0.015	0.05
Met	0.064	0.007	0.11
Cys	0.025	0.017	0.68
Phe	0.096	0.151	1.57
Tyr	0.088	0.939	10.67
Pro	1.075	0.381	0.35
His	65.274	33.158	0.51
Ser	1.619	14.804	9.14
Thr	11.217	1.257	0.11
Glu	52.523	8.552	0.16
Asp	4.579	11.758	2.57
Lys	2.885	3.604	1.25
Arg	42.149	40.592	0.96

SOURCE: Reprinted with permission from ref. 2. Copyright 1990.

The value of (C) and (R) represent the amounts of intracellular amino acid expressed as nmol/2x10^8 cells without and with RI-331 (15 μg/ml)-treatment, respectively. The value of R/C indicates the ratio of (R) to (C).

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

Interestingly, these three amino acids, together with aspartate, are known to be metabolized through the same metabolic pathway in prototrophic microorganisms (Fig. 3). Then, we asked if the reduction of these amino acids in RI-331-treated yeast cells is responsible for the antifungal action of the antibiotic. To answer this question, the antagonistic effect of each amino acid on anti-*Saccharomyces* action of RI-331 was tested. The addition of methionine, threonine, isoleucine and their intermediate precursor homoserine to the chemically defined culture medium markedly reversed the antifungal action of RI-331. Homoserine showed a particularly strong reversing effect (Table III).

Table III. The Antagonistic Effect of Several Amino Acids on the Growth Inhibitory Activity of RI-331 against *Saccharomyces cerevisiae*

Amino acid added	IC_{50} of RI-331 (μg/ml)	Degree of reversion
None (control)	1.7	1.0
Gly	2.5	1.5
Ala	2.5	1.4
Val	2.9	1.7
Leu	2.1	1.2
Ile	6.3	3.7
Met	12.5	7.4
Phe	2.8	1.6
Pro	2.0	1.2
Ser	4.8	2.8
Thr	9.9	5.8
Homoserine	50.0	29.4
Asp	2.0	1.2
Asn	6.6	3.9
Glu	2.4	1.4
Gln	3.7	2.2
Arg	1.9	1.1
Lys	1.9	1.1

SOURCE: Reproduced with permission from ref. 2. Copyright 1990.

The value of IC_{50} of RI-331 was determined on the basis of the optical density of cultures.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

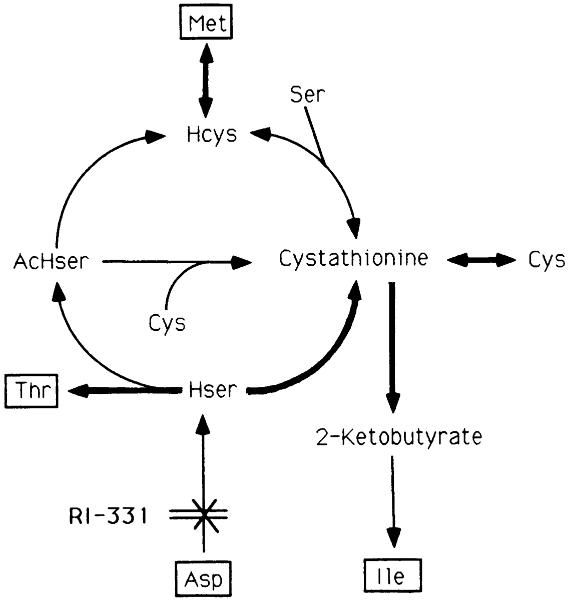

Met
Ser
Hcys
AcHser
Cystathionine
Cys
Cys
Thr
Hser
2-Ketobutyrate
RI-331
Asp
Ile

Figure 3. Biochemical pathway involved in metabolism of the aspartate family of amino acids in prototrophic fungi and the assumed site of action of RI-331. The marks are shown as follows: ➡ General, → defective in mammals, and essential amino acids for mammals are boxed. Abbrevations: Hser, homoserine; AcHser, acetylhomoserine. (Adapted from ref. 2).

These results therefore suggested that RI-331 acts on some step(s) involved in the pathway converting aspartate to homoserine.

Inhibition of Homoserine Dehydrogenase. In order to investigate details of the target site of RI-331 action, enzymatic studies were performed by using a cell-free preparation from a strain of *S. cerevisiae* prototrophic in the pathway responsible for converting aspartate to homoserine. In the enzymatic conversion of aspartate into homoserine, 1 mole of ATP and 2 moles of NADPH are consumed (Fig. 4). The rate of the reaction depending on added aspartate and ATP can be monitored by the decrease in absorbance at 340 nm as NADPH disappears. The rate of NADPH consumption was significantly inhibited by the antibiotic, indicating the inhibition of conversion of aspartate to homoserine (3). In the conversion of aspartate to homoserine three enzymes aspartate kinase, aspartate semialdehyde dehydrogenase and homoserine dehydrogenase are involved (Fig. 4).

To further examine the sensitivity of these enzymes to the antibiotic, we purified these enzymes using mutant strains of *S. cerevisiae*, blocked in the pathway from aspartate to homoserine. Aspartate kinase was purified from the hom2 mutant, S2614C, (lacking aspartate semialdehyde dehydrogenase) by the method as described (4). Aspartate semialdehyde dehydrogenase was purified from the hom6 mutant, STX25-2A, (lacking homoserine dehydrogenase), and homoserine dehydrogenase was purified from the hom2 mutant, S2614C as described (5,6).

The former two enzymes, aspartate kinase and aspartate semialdehyde dehydrogenase, were refractory to the antibiotic, and the last enzyme, homoserine dehydrogenase was significantly sensitive to RI-331.

Homoserine dehydrogenase activity in the forward reaction, determined by NADPH dehydrogenation and dependent on the added substrate aspartate semialdehyde (ASA), was significantly inhibited by the antibiotic. The inhibition of the enzyme activity was enhanced if NADP was added to the reaction mixture at high concentrations relative to NADPH (Fig. 5), even although NADP is not required in the forward reaction. The rate of the forward reaction of the control (without RI-331) was not affected by addition of NADP. These results presumably indicate that RI-331 inactivates the enzyme by interacting with the enzyme-NADP complex. The inhibition was the mixed type of competitive and noncompetitive inhibition with respect to ASA with a

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

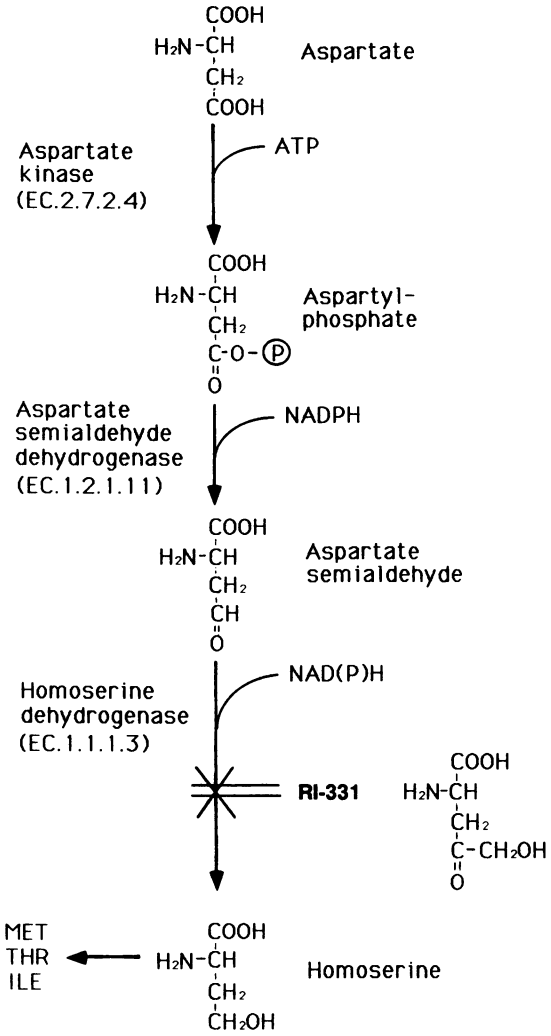

COOH
H2N-CH
CH2
COOH
Aspartate
Aspartate kinase (EC.2.7.2.4)
ATP
COOH
H2N-CH
CH2
C-O-Ⓟ
O
Aspartyl-phosphate
Aspartate semialdehyde dehydrogenase (EC.1.2.1.11)
NADPH
COOH
H2N-CH
CH2
CH
O
Aspartate semialdehyde
Homoserine dehydrogenase (EC.1.1.1.3)
NAD(P)H
RI-331
COOH
H2N-CH
CH2
C-CH2OH
O
MET
THR
ILE
COOH
H2N-CH
CH2
CH2OH
Homoserine

Figure 4. Biochemical pathway from aspartate to homoserine, and the target site of RI-331 (Adapted from ref. 3).

Ki value of 2 mM vs a Km value of 0.05 mM at a physiological concentration of NADP (0.2 mM), and the reaction was inhibited at high concentrations (> 0.04 mM) of the substrate ASA itself (Fig. 6). The inhibition of this forward reaction by the antibiotic was noncompetitive with respect to NADP, and the association constant for NADP in the presence of the antibiotic revealed two values of 0.4 and 2 mM as analyzed by Dixon-plot (Fig. 7) (Yamaki, H., J. Antibiotics, in press), suggesting that the enzyme might interact with the antibiotic in two ways to give ternary complexes (enzyme, NADP and antibiotic) of differing stabilities.

Homoserine dehydrogenase was more sensitive to the antibiotic in the reverse reaction than in the forward reaction. The inhibition was competitive with respect to the substrate homoserine showing a Ki value of 0.025 mM vs Km value of 17 mM (Fig. 8) (Yamaki, H., J. Antibiotics, in press). Moreover, prior exposure of the enzyme to NADP before starting the reaction enhanced the extent of inhibition of the enzyme in the reverse reaction (Yamaki, H., J. Antibiotics, in press). The possibility that the enzyme-NADP complex is formed first, then interacts with the antibiotic, leading to inactivation of the enzyme (Fig. 9), can be supported by the high degree of inhibition of the enzyme by the antibiotic in the reverse reaction in which enzyme-NADP complex formation is an essential step of the reaction (Fig. 8). The experimental data could be explained if binding of NADP were to induce a conformational change in the enzyme which facilitates binding of the antibiotic, and causes an accumulation of the inactive enzyme-NADP-RI-331 complex in antibiotic -treated yeast cells resulting in decreasing enzyme activity.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

Growth Inhibition of Plant Pathogenic Fungi by RI-331.

We found that the antibiotic markedly inhibits the growth of *Cladosporium fulvus* which is a pathogen of tomato leaf mold disease (Fig. 10), but not that of *Chrollera* spp., suggesting that the antibiotic selectively inhibits certain pathogenic fungi, and is possibly useful as antifungal agrochemicals.

Discussion.

A large number of amino acid analogs have been developed as antimetabolites so far, some of which exhibit anti-

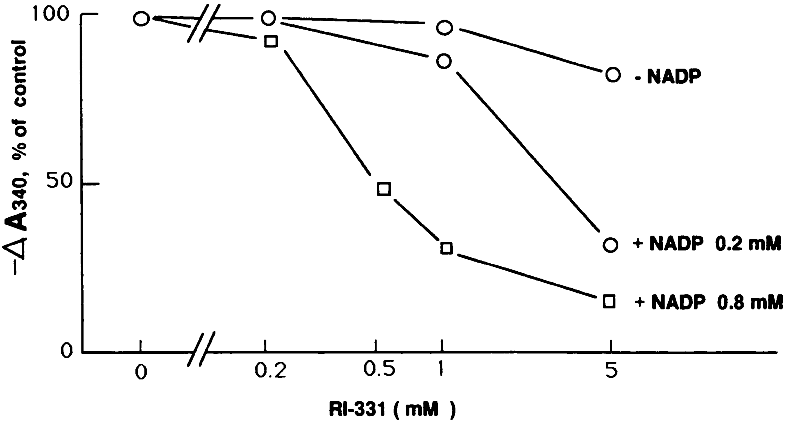


Figure 5. Influence of NADP concentration on the inhibition of homoserine dehydrogenase activity in the forward reaction by RI-331. (Reproduced from J. Antibiotics 1992 45 in press).

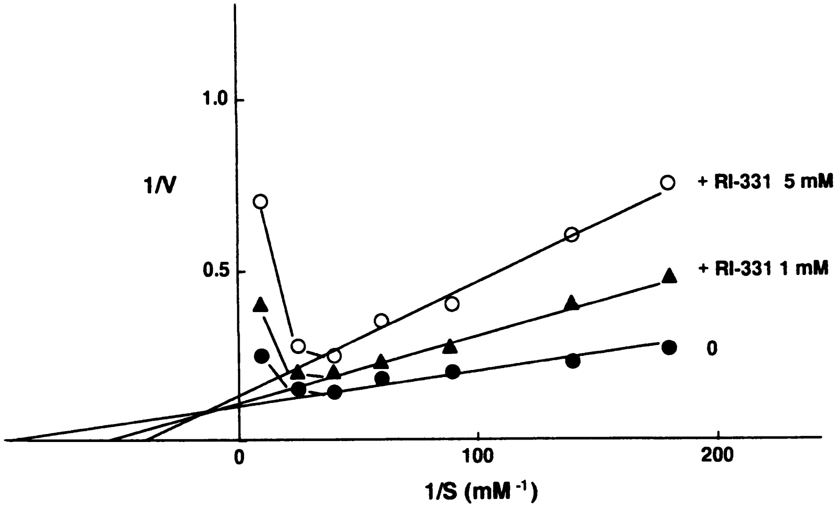


Figure 6. Lineweaver-Burg plot of the inhibition by RI-331 of homoserine dehydrogenase in the forward reaction with respect to the substrate, aspartate semialdehyde. (Reproduced from J. Antibiotics 1992 45 in press).

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

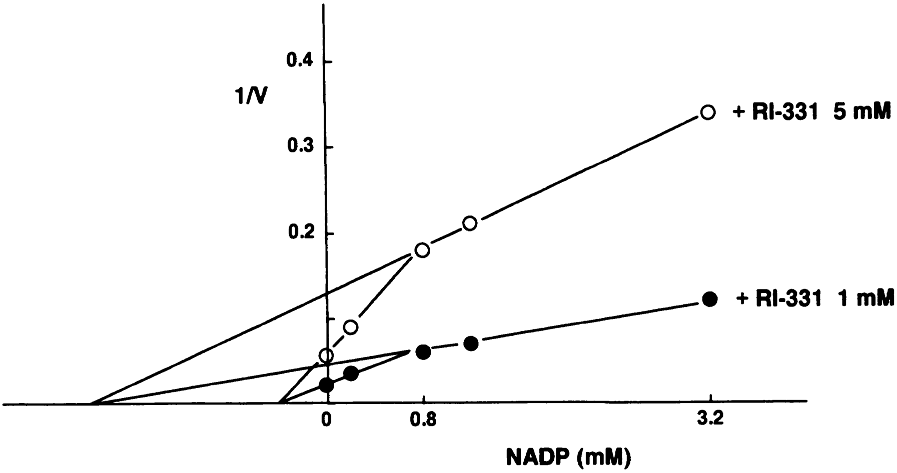


Figure 7. Dixon-plot of the inhibition by RI-331 of homoserine dehydrogenase in the forward reaction with respect to NADP. (Reproduced from J. Antibiotics 1992 45 in press).

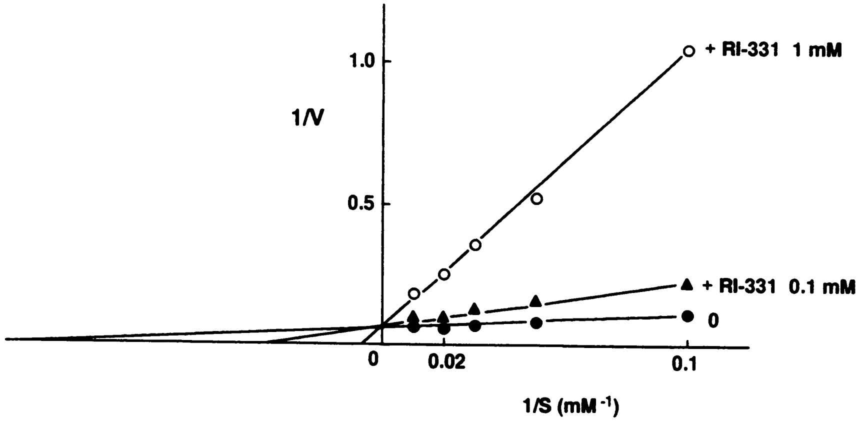


Figure 8. Lineweaver-Burg plot of the inhibition by RI-331 of homoserine dehydrogenase in the reverse reaction with respect to the substrate, homoserine. (Reproduced from J. Antibiotics 1992 45 in press).

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

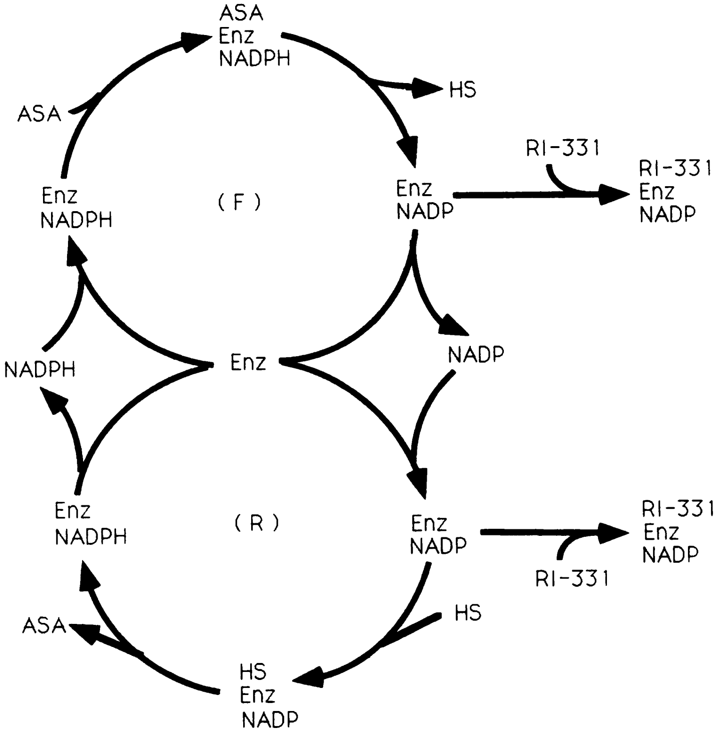

ASA
Enz
NADPH
HS
ASA
Enz
NADPH
(F)
Enz
NADP
RI-331
RI-331
Enz
NADP
NADPH
Enz
NADP
Enz
NADPH
(R)
Enz
NADP
RI-331
Enz
NADP
RI-331
ASA
HS
HS
Enz
NADP

Figure 9. Scheme of enzyme-substrate complex in homoserine dehydrogenase reaction, and an assumed mode of interaction of RI-331 with enzyme. Abbrevations: Enz; homoserine dehydrogenase from S. cerevisiae, ASA; aspartate semialdehyde, HS; homoserine, (F); forward reaction, (R); reverse reaction. (Reproduced from J. Antibiotics 1992 45 in press).

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

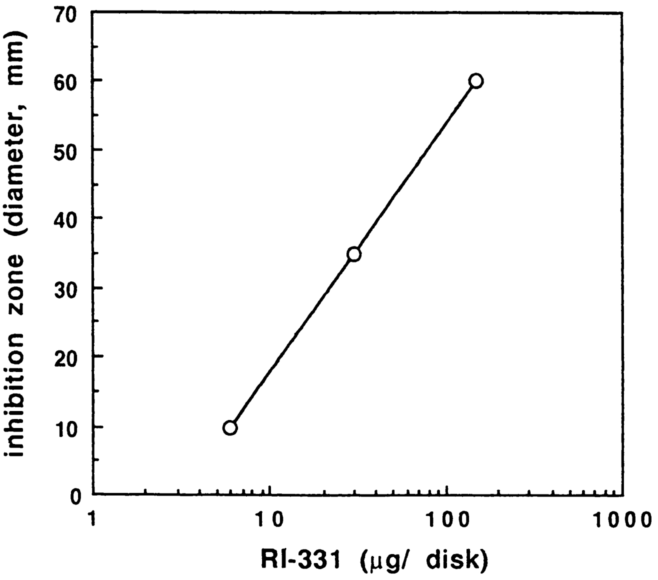


Figure 10. The growth inhibition of *Cladosporium fulvus* by RI-331. *C. fulvus* was cultured in agar plate of YNB w/o amino acid medium and the inhibition zone was detected by paper-disk assay.

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

fungal activity. The majority of effective compounds have been chemically synthesized, although some were natural products, isolated either as antibiotics or substances toxic to animals (7,8). We are able to find out the inhibitor of biosynthesis of essential amino acids among the compounds reported previously. We are interested in whether the inhibitors of homoserine dehydrogenase from Escherichia coli which have been reported previously, 2-amino-4-oxo-5-chloropentanoate (9) and β-hydroxynorvaline (10), could be useful for antifungal agent. Inhibitor of the biosynthesis of essential amino acids for animals other than threonine, isoleucine and methionine is also of our interst, asking whether such inhibitor could be useful for antifungal chemotherapy or as antifungal agrochemicals. Also It should be worthy of searching for antifungal agrochemicals out of antifungal agents of medical use.

Acknowledgments

We are indebted to Drs. S. Omura, T. Nagate, H. Fukushima, and C. Yokoo, Taisho Pharmaceutical Co., Ltd., Ohmiya, Saitama Prefecture, Japan, and Dr. H. Saito, Teikyo University, Hachioji, Tokyo, Japan for their valuable discussion of this work. This work was supported by a Japanese Antibiotics Research Association Research Grant.

Literature Cited.

1. Yamaguchi,H.; Uchida,K., Hiratani,T., Nagate,T., Watanabe,N. & Omura,S. Ann.N.Y.Acad.Sci.1988,544, 188-190.
2. Yamaguchi,M.; Yamaki,H., Shinoda,T., Tago,Y., Suzuki,H., Nishimura,T. & Yamaguchi,H. J.Antibiotics 1990,43,411-416.
3. Yamaki,H.; Yamaguchi,M., Imamura,H., Suzuki,H., Nishimura,T., Saito,H. & Yamaguchi,H. Biochem.Biophys. Res.Commun.1990,168,837-843.
4. Black,S.; Wright,N.G. J.Biol.Chem.1955,213,27-38.
5. Black,S.; Wright,N.G. J.Biol.Chem.1955,213,39-50.
6. Black,S.; Wright,N.G. J.Biol.Chem.1955,213,51-60.
7. Shive,W.; Skinner,C.G. In Amino acid analogues; Hochster,R.M. & Quastel,J.H.,Ed.,Metabolic Inhibitors; Academic Press: New York,1963, Vol. 1; pp 1-58.

8. Fowden,L.; Lewis,D. & H. Tristram: In Toxic amino acids. Their action as antimetabolites; In Advances in Enzymology; Nord,F.F., Ed.; Interscience Publishers: New York,1967, Vol. 29; pp 89-163.
9. Hirth,C.G.; Veron,M., Villar-Parasi,C., Hurion,N. & Cohen,G.N. Eur.J.Biochem.1975,50,425-430.
10. Cohen,G.N.; Patte,J-C., Truffa-Bachi,P., Sawas,C. & Doudoroff,M. Mecanismes de regulation des activites cellulaires chez les microorganismes; Colloques Intern.C.N.R.S.: Paris,1965; Vol. 124, pp 243-258.

RECEIVED April 27, 1992

Downloaded by STANFORD UNIV GREEN LIBR on June 22, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch039

Chapter 40

A Novel Class of Benzamide Fungicides

David Bartholomew, Patrick J. Crowley, and I. Trevor Kay

ICI Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY, United Kingdom

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

A new class of fungicides was discovered as a result of speculative chemistry carried out in an attempt to make novel cyano imines. The products of trapping these imines with alcohols turned out to have interesting fungicidal and herbicidal activity. After a careful study of the structure activity relationships (SAR), highly active fungicides were found for the control of Oomycete fungi, and the compound 4-chloro-N-[cyano(ethoxy)methyl]benzamide was chosen as a development candidate. The origins of the work, the synthetic chemistry, SAR, and physical properties of the compounds are described and, the mode of action and resistance properties of the compounds are briefly discussed.

There are a number of approaches to the discovery of agrochemicals. Those usually discussed include random screening, patent following, using natural products as the basis for invention, and biochemically oriented rational design. One approach often omitted however, is the use of blue-sky or speculative chemistry, probably because it has connotations of randomness or lack of design. Although this may be the case, blue-sky research does enable the chemist to break free from the restrictions of imitative chemistry and can lead to the generation of truly novel classes of biologically active molecule. The invention of the benzamide fungicides described in this paper provides an example of the successful application of this approach.

There are perhaps two ways of using speculative chemistry in the inventive process. One is the exploration of a piece of chemistry for its intrinsic interest, perhaps to provide examples of a novel type of compound for testing. The other is the deliberate investigation of a chemical idea that the chemist believes may lead to some biological activity. The benzamide fungicides described here are a product of a combination of both approaches. The original idea was stimulated by a piece of pure chemical exploration, while the exploitation of that idea was planned to search for biological activity.

0097–6156/92/0504–0443$06.00/0

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

Origins of the Work

In the late 1970's, Drs. I. T. Kay and D. Bartholomew, working at ICI Agrochemicals, were exploring the chemistry of chlorocarbonyl sulfamoyl chlorides, a novel class of heterocyclic precursor which they had developed earlier (*1*).

Using the sulfamoyl chloride **1** (Figure 1), they had built up the new ring system **2** and in turn were exploring the chemistry of this heterocycle. Attempts to alkylate **2** with chloroacetonitrile to give **3**, gave instead thiatriazinone **6** (*2*). The reaction was postulated to involve ring opening to generate the reactive cyano imine **4**, which was then trapped intramolecularly to give **5**. Elimination of cyanide then gave **6**.

On consideration of the mechanism they wondered whether cyano imines of this type (or compounds which could generate them), could be isolated, and whether they might show biological activity. As amide groups and benzene rings are frequently found in biologically active molecules they chose to make some simple model compounds incorporating both these functionalities and the cyano imine. The first target was **9**.

Treatment of benzoylaminoacetonitrile with t-butyl hypochlorite gave the N-chloro amide **7**. It was hoped that on irradiation **7** would rearrange to the C-chloro amide **8**, which would in turn eliminate hydrogen chloride to give the imine **9**. The reaction was carried out and worked up by treatment with aqueous methanol. Instead of chloride **8**, the methoxy compound **10** was obtained, albeit in low yield (Figure 2).

Biological testing of **10** gave a weak herbicidal signal. This was encouraging enough to carry out further work, to produce more material and to develop a better route for the synthesis of analogues.

Herbicide and Fungicide Structure Activity Relationships

Early Work. The first set of analogues exhibited both herbicidal and fungicidal activity. The fungicidal activity was interesting principally because of the activity on the Oomycete pathogens, *Plasmopara viticola* and *Phytophthora infestans*, but the high phytotoxicity of the compounds seemed to rule out their use as fungicides. Attention was therefore concentrated on optimising the promising herbicidal activity.

Quite quickly the herbicidal symptomology was recognised as being similar to that of the Rohm and Haas herbicide propyzamide **11**. A search of the literature revealed that the SAR for propyzamide and analogues had been published (*3*), and that 3,5-disubstitution in the benzene ring was optimum for herbicidal activity. Using this information it was quickly demonstrated that the same substitution pattern held in the new series with **12** having interesting herbicidal activity (Figure 3).

There were, however, significant differences between the new series and the Rohm and Haas amides, (see Table I for a summary of the structure activity relationships). Most important was the presence of the cyano group, which gave greatly enhanced herbicidal activity over the acetylene in propyzamide, and was found to be essential for fungicidal activity. The corresponding amides and esters were poor as herbicides and inactive as fungicides, although most of the activity was retained with the thioamides. Highest activity was obtained with short saturated or unsaturated alkoxy groups, with ethoxy being optimal. Interestingly the analogue of propyzamide with the acetylene replaced by a nitrile was very poorly active. The analogous sulfides

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

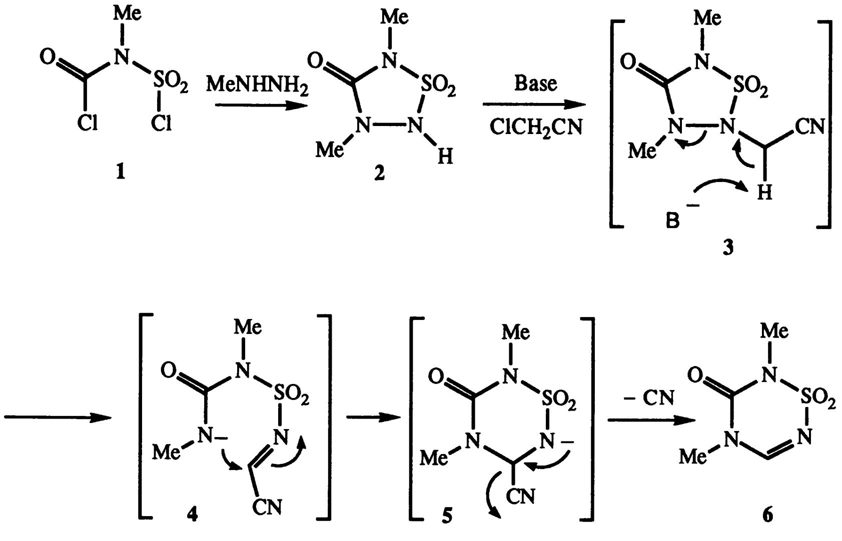

1
MeNHNH2
2
Base
ClCH2CN
3
B⁻
4
5
- CN
6

Figure 1

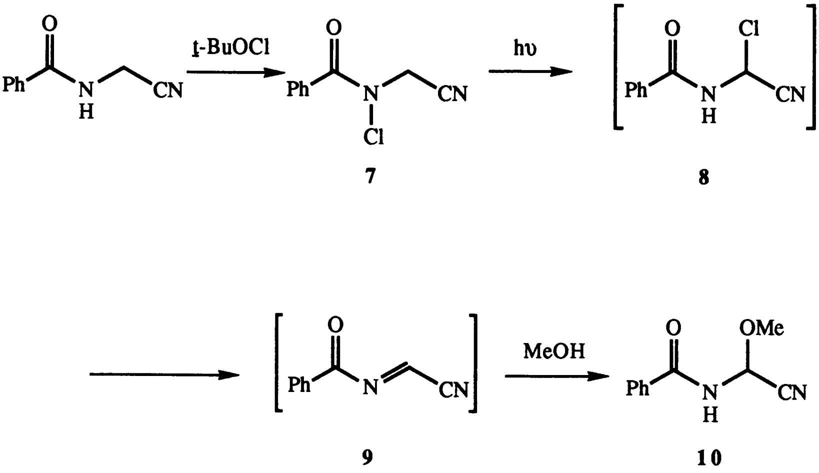
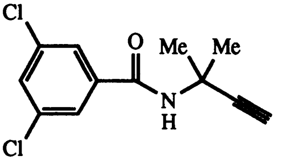
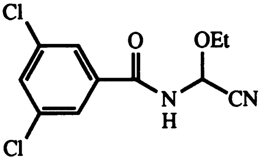

t-BuOCl
7
hυ
8
9
MeOH
10

Figure 2

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040



11

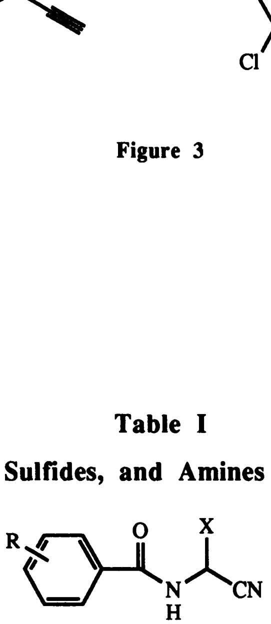


12

Figure 3

Table I

Activity of Ethers, Sulfides, and Amines on *Plasmopara viticola* *



	HIGH (<10 ppm)	MED. (10-50 ppm)	LOW (>50 ppm)
Position of R**	3,5- > 3- ≥ 4-		2-
R**	Cl > Me , Br	F > MeO	CF_3 >> PhO , NO_2 , NH_2
X**	OEt > OMe , SMe > O-propargyl>O-allyl	O-n-Pr > O-n-Bu , O-t-Bu > OPh	NHAr , $S(O)_{1-2}$ Me , NHAc , Me

* = foliar spray or root drench on vines ; lowest rate giving 100% control

** = order of activity generally independent of other variables were quite active, but the simple alkylamino analogues were too unstable to be isolated. The corresponding anilines were isolable but had very poor activity. It was found that the order of activity for any individual variable (the side chain substituent X, the substituent R, or its position in the benzene ring) in the general structure in Table 1, was usually independent of the other variables.

Attempts were made to broaden the range of active structural types, but herbicidal and particularly fungicidal activity was limited to a narrow group of structures. For example, replacement of the benzene ring with heterocycles such as substituted pyridine reduced activity markedly, while replacement with alkyl groups removed activity completely. Insertion of additional atoms between the aromatic ring and the amide carbonyl led to completely inactive compounds, while other variations such as the reversal of linkages and replacement of heteroatoms by carbons, met with a similar lack of success (Figure 4).

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

Variations in the Amide Side Chain. At the time we were very actively researching the azole sterol inhibitors, and it was interesting to see if activity on Oomycete and cereal pathogens could be combined in one molecule. Attempts were made to replace the alkoxy group by imidazole, but the compounds were too unstable to isolate. The 1,2,4-triazoles were more stable, but unfortunately suffered the usual fate of hybrid toxophores, being poorly active on all fungi. However, as an extension of this work some pyrazoles were made. These turned out to have the highest herbicidal and fungicidal activity of all of the series (see Table II).

However, following the outstanding activity of the pyrazoles, further 5-membered heterocycles were tried. Activity was well down for other nitrogen rings such as 1,2,3-triazole (symmetrical isomer) or tetrazole (2-isomer). Interestingly however, good activity was maintained, although at a slightly lower level, when furan or thiophene linked either in the 2- or 3-position were used, with the furans usually being slightly more active than the corresponding thiophenes. Later work by other companies showed that high activity could also be achieved with thiophenes of this type when the benzene ring was replaced by a substituted pyrazole (*12*). Other C-linked heterocycles such as the 2-pyrrolyl , or 2-thiazolyl analogues were inactive.

The activity of all the five-membered ring compounds was very sensitive to substitution. Even a methyl group reduced activity significantly, while the presence of more, or larger groups destroyed it. Replacement of five-membered rings by six-membered rings such as phenyl or pyridyl led to complete inactivity. A summary is given in Table II.

Fungicidal Activity and Phytotoxicity.

Although the best compounds had high levels of intrinsic herbicidal activity, their lack of selectivity and relatively poor stability in soil prevented their development as herbicides.

However, there was considerable interest in the high systemic fungicidal activity some of these compounds exhibited on the Oomycete pathogens *Plasmopara viticola* and *Phytophthora infestans*, despite the evident phytotoxicity. This interest was boosted by an early field test of **12** on *Plasmopara viticola*, which showed that promising control of disease could be obtained, although the trial was stopped early to prevent damage to the vines.

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

STRUCTURAL CHANGES LEADING TO LOW ACTIVITY

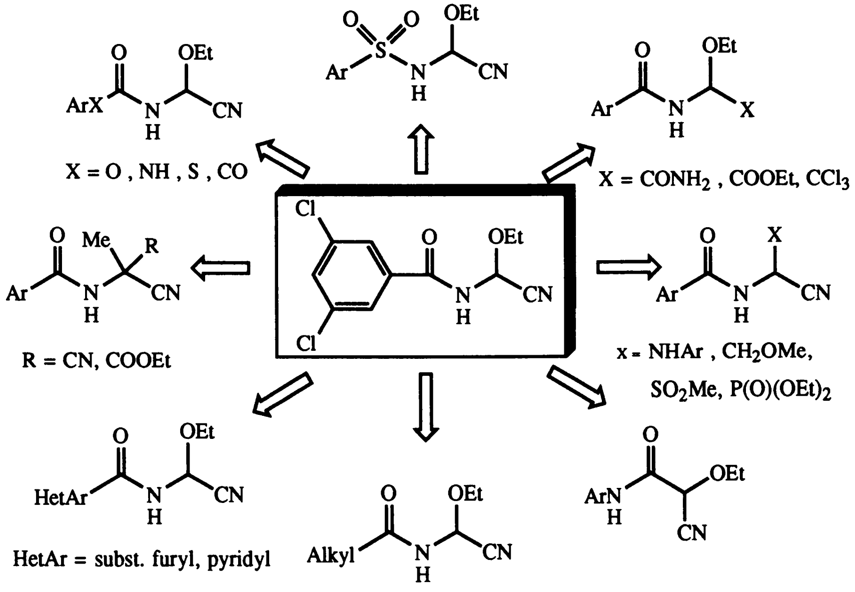
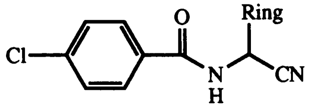
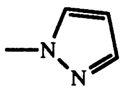
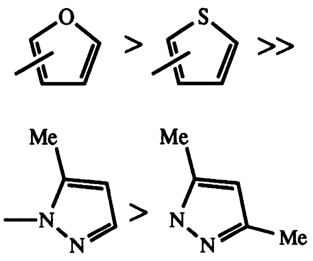
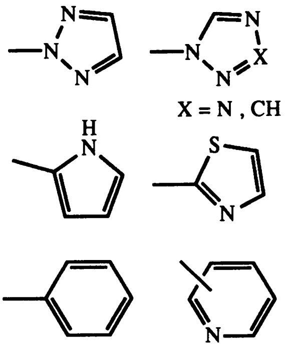

X = O , NH , S , CO
X = CONH2 , COOEt, CCl3
R = CN, COOEt
x = NHAr , CH2OMe, SO2Me, P(O)(OEt)2
HetAr = subst. furyl, pyridyl

Figure 4

Table II: Activity of Side Chain Ring Compounds*



HIGH (<5 ppm)	MEDIUM (5-50 ppm)	LOW (>50 ppm)
		

* as foliar spray or root drench on *Plasmopara viticola* on vines

It was clearly critical to the success of these compounds as fungicides for their phytotoxicity to be reduced. It was found that the presence of a single substituent in the 4-position of the benzene ring preserved very good levels of fungicidal activity, and greatly reduced herbicidal effects, depending on the identity of X (see Table I). However, this was only the case with small, relatively non-polar and linear substituents such as halogen, short alkyl, ethynyl, methoxyimino and methoxymethyl groups. Polar (eg. nitro or hydroxy), or bulky (eg. phenyl, phenoxy) groups reduced activity markedly, while the presence of a sustituent in the 3-position brought back herbicidal activity. Interestingly the 4-formyl and 4-hydroxymethyl analogues were the only compounds to show reasonable activity on the soil-borne pathogen *Pythium ultimum*. A summary is provided in Table III.

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

ICIA0001

The pyrazoles, although highly active, were generally too phytotoxic to use, while the furans were not active enough to be cost effective. However, the combination of the ethoxy side chain and 4-substitution in the ring gave a small group of compounds which had both high fungicidal activity and good crop safety. Of these, 4-chloro-N-[cyano(ethoxy)methyl] benzamide **13**, was chosen as a development candidate with the code number ICIA0001, and subsequently given the common name zarilamide (Figure 5).

Despite the possible lability of the hydrogen adjacent to the cyano and ethoxy groups, separation of the R- and S- enantiomers of ICIA0001 was achieved by chiral chromatography, on a preparative scale. It was found that virtually all the biological activity resided in a single enantiomer, but it was not known which.

Biological Activity. Details of the biological activity of ICIA0001 have been published previously (*4*), and so a brief summary only is provided here.

Excellent activity was obtained in field trials on a range of Oomycete fungi, particularly *Plasmopara viticola* on both berries and foliage. The compound was usually mixed with a protectant standard such as folpet to enhance persistence of control and to reduce the risk of resistance developing. Good control was also achieved on *Phytophthora infestans* on potatoes and tomatoes, *Pseudoperonospora humuli* on hops, *Pseudoperonospora cubensis* on cucurbits, and *Phytophthora palmivora* on cocoa. Under a wide range of conditions a good margin between fungicidal activity and phytotoxicity was found.

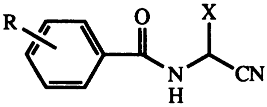
ICIA0001 also had excellent environmental properties. Residues on grapes were exceptionally low and degradation in soils was rapid and total. The compound had little soil mobility.

Physical Properties and Plant Movement.

Systemic movement is a very desirable property for compounds active on the Oomycete fungi, as it enables control of disease in new growth. Some of these compounds showed good plant mobility, but only where the log P was below about 2.8. This is shown in Table III, where, for example, changing from mono- to dichloro-substitution in the benzene ring tips the balance from activity by root drench application, to activity by foliar spray only.

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

Table III: Activity and Phytotoxicity of Leading Compounds *

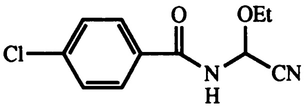


R	X	PLASVI **		PHYTIN **	PHYTO.***	LOG P
		Foliar	Root Drench	Foliar		
3,5-di-Cl	1-Pyrazolyl	<1	>25	1	10	3.28
3,5-di-Cl	OEt	5	>25	2.5	25	2.90
4-Cl	1-Pyrazolyl	3	1	<1	30	2.51
4-Cl	OEt	30	3	10	>100	2.6
4-Cl	2-Furyl	10	10	>25	>500	2.8
4-Ethynyl	OEt	10	5	10	100	2.4[e]

* lowest rate (ppm) giving 100% control *** Lowest rate (ppm) where symptoms noted

* *Plasmopara viticola on vines, Phytophthora infestans on potatoes

[e] estimated value



13

Figure 5

Pro-pesticides.

Thioamide was the only functional group apart from nitrile that gave rise to good activity. The equivalence of nitriles and their corresponding thioamides has frequently been observed in biological chemistry, and is thought to be due to chemical or metabolic conversion of the thioamide to the nitrile. Some supporting evidence for this was provided in this series by the fact that significant amounts of nitrile **14** were produced when a dilute aqueous solution of thioamide **15** was heated at pH 7. It was hoped that differential metabolism of **15** between the fungus and the plant might maintain fungicidal activity and lower phytotoxicity. This would allow the use of the more active but more phytotoxic pyrazoles, as their thioamides. However, this was not the case, and both control of disease and plant damage were equally reduced.

Another approach to reducing phytotoxicity was to use lipophilic protecting groups, which might be selectively cleaved in the fungus to liberate the active fungicide. Accordingly some N-benzenesulphenyl compounds **16** were made (Figure 6), but again crop safety was only achieved at the expense of fungicidal activity.

Involvement of Reactive Intermediates.

Since this project had arisen from ideas about reactive imines, it was of interest to see whether evidence could be found to support their existence, or their possible role in the activity of these fungicides. Information came from two sources.

Firstly, analysis of the structure activity relationships showed that only compounds which were capable of producing potentially reactive imines had significant activity, (figure 7). Those which could not eliminate a leaving group to give a reactive imine, for example the N-methyl analogues **20**, were inactive. The fact that **17**, where X=furan, can only eliminate cyanide, suggests that only imine **19**, could play a part, at least in the case of the furans. However, the inactivity of the sulphide **23**, which had the potential to generate **19**, showed that imine formation might not be involved in the activity. A possible alternative explanation was that cyanide, released in the elimination process, might be the ultimate toxic agent. However, evidence from biochemical experiments suggested that cyanosis was not involved in the mode of action.

Secondly, results from studies on the hydrolytic breakdown of **17** suggested that imines **18** and **19** could be formed chemically. Over a range of pH, **17** (X=ethoxy, furan or pyrazole) was shown to break down to the simple benzamide **22** with the formamide **21** as an intermediate. Formamide **21** could arise from addition of water to either **18** or **19**, followed by elimination of X or CN. Compounds **17** where X=OEt were found to be the least stable, particularly at high pH where the amide anion would be expected to be formed. The presence of electron-withdrawing groups in the benzene ring of **17** accelerated breakdown, supporting formation of the amide anion as the rate-determining step. Compounds **17** where X=pyrazole were of intermediate stability, but underwent acid catalysed breakdown at low pH, when protonation of the pyrazole could occur. Compounds **17** with X=furan were the most stable, at all pH values, showing that chemical loss of cyanide was slow.

From the information available it was not possible to come to a conclusion about the role of imine intermediates. The stability studies may be relevant to the persistence of the compounds rather than their mode of action.

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

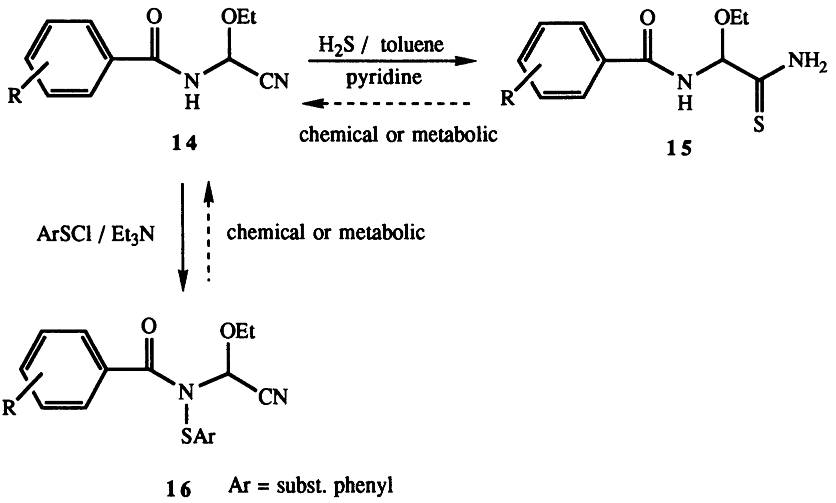

O
OEt
N
H
CN
R
14
H$_2$S / toluene
pyridine
chemical or metabolic
NH$_2$
S
15
ArSCl / Et$_3$N
chemical or metabolic
SAr
16
Ar = subst. phenyl

Figure 6

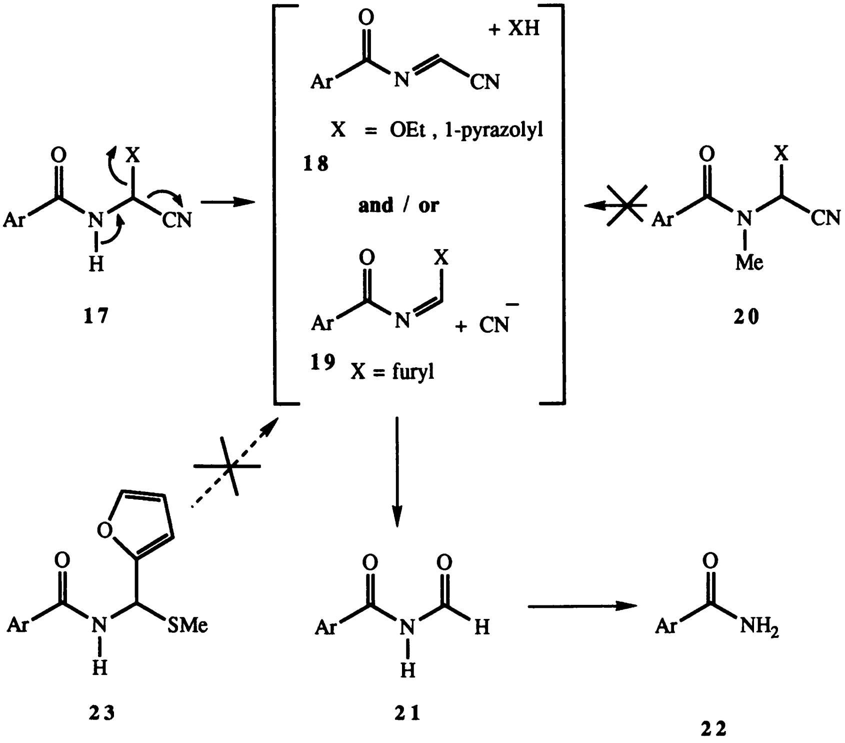

Ar
O
X
N
H
CN
17
+ XH
X = OEt, 1-pyrazolyl
18
and / or
+ CN$^-$
19
X = furyl
Me
20
SMe
23
H
21
NH$_2$
22

Figure 7

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

Synthetic Routes

The original route using photochlorination of the benzoylaminoacetonitrile **24** was not found to be generally useful, and alternative approaches were sought. Initially, attempts at direct bromintion of **24**, and reaction with nucleophiles to give **28** gave only intractable mixtures. However, it was found that in acetic acid, bromination of **24** gave the isolable bromoamides **26**, formed by in situ hydration, possibly of an oxazole intermediate **25**. Displacement of the bromine with nucleophiles gave amides **27**, which were dehydrated to give good yields of the nitriles **28**, (*5*). This proved a versatile, if slightly lengthy route by which many analogues were made, (Figure 8).

Later it was shown that direct bromination of **24** to give bromonitrile **29** could be achieved (*6*), but only under highly specific conditions, whereby the bromine was added very rapidly. Due to its high reactivity it was necessary to treat **29** with ethanol in situ, to obtain **31**. Although not high yielding, this direct route enabled rapid synthesis of further analogues.

On a large scale, where rapid bromination was a problem, development work showed that on treatment of **29** with pyridine in situ, the reasonably stable pyridinium salt **30** could be isolated (*7*), which could then be treated with ethanol in a separate step to give **31**, (figure 9).

Synthesis of the furans and thiophenes **33**, was straightforward from the corresponding amino nitriles, which were readily available using the Strecker reaction on the aldehydes. An alternative route was developed to the 2-linked furans and thiophenes (*5*), whereby acetoxy ester **34** was treated with a Lewis acid and furan or thiophene to give the ester **35**, in an amido-alkylation reaction. **35** was then converted to nitrile **37** after conversion to the amide **36**, (Figure 10).

During the synthesis of analogues, a wide variety of substituted benzenes were required. Most of these were obtained straightforwardly. Of note, however, was the synthesis of the acetylenic analogues **39**, which were made in good yield from the iodo compounds **38**, by palladium-catalysed coupling with the corresponding acetylenes (*8*). It was necessary to carry out the reaction in triethylamine as solvent, to avoid reaction with the more usually used diethylamine, (figure 11).

Mode of Action

ICIA0001 showed no effects in a range of standard biochemical tests such as respiration, or DNA and RNA synthesis assays. Later studies (*9, 10*) showed that ICIA0001 affects microtubules in tobacco cells, and in zoospores of *Phytophthora capsici*, with consequent inhibition of mitosis. Propyzamide showed similar effects in tobacco cells, which is consistent with the similarity in herbicide symptomologies between the two compounds.

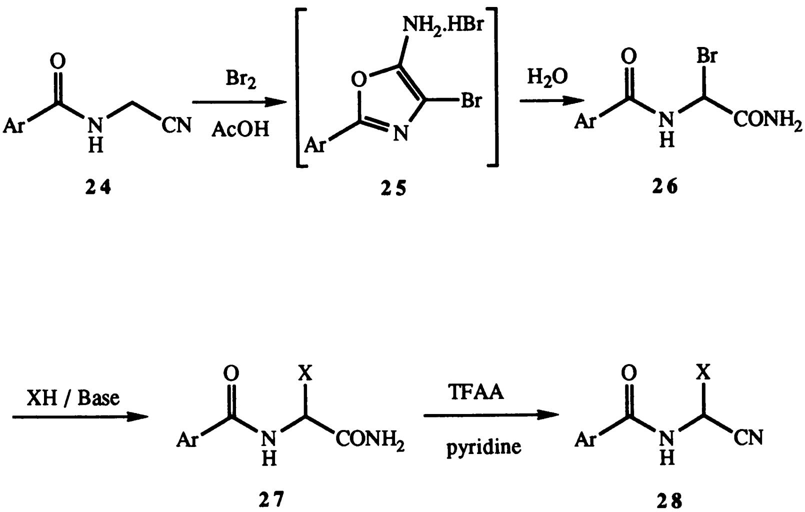
Resistance Properties

It is currently essential to the development of any new Oomycete fungicide that it should be able to control disease that is resistant to the phenyl amide fungicides (for example metalaxyl). It is also desirable to estimate the potential for the development of resistance in any new molecule.

Detailed studies (*11*) carried out with ICI0001 on *Phytophthora* spp. showed

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040


Br2
AcOH
H2O
XH / Base
TFAA
pyridine
24
25
26
27
28

X = OR (R = alkyl , alkenyl, alkynyl) , SR , 1-pyrazolyl , etc.

Figure 8

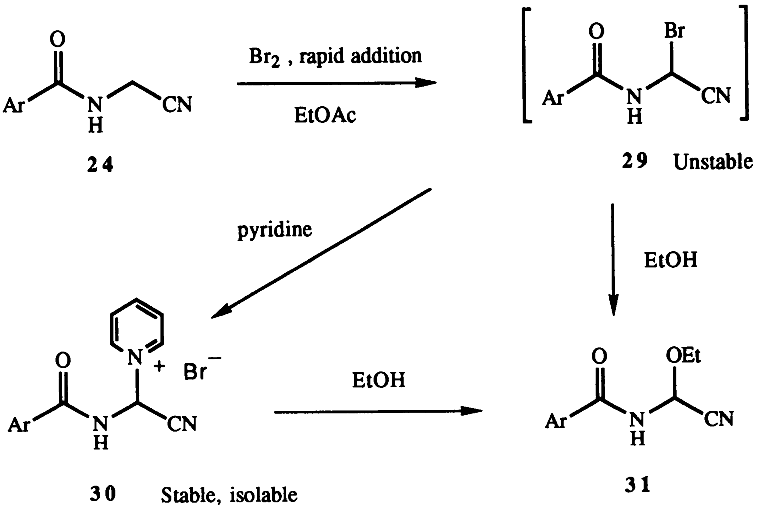

Br2 , rapid addition
EtOAc
pyridine
EtOH
EtOH
24
29 Unstable
30 Stable, isolable
31

Figure 9

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

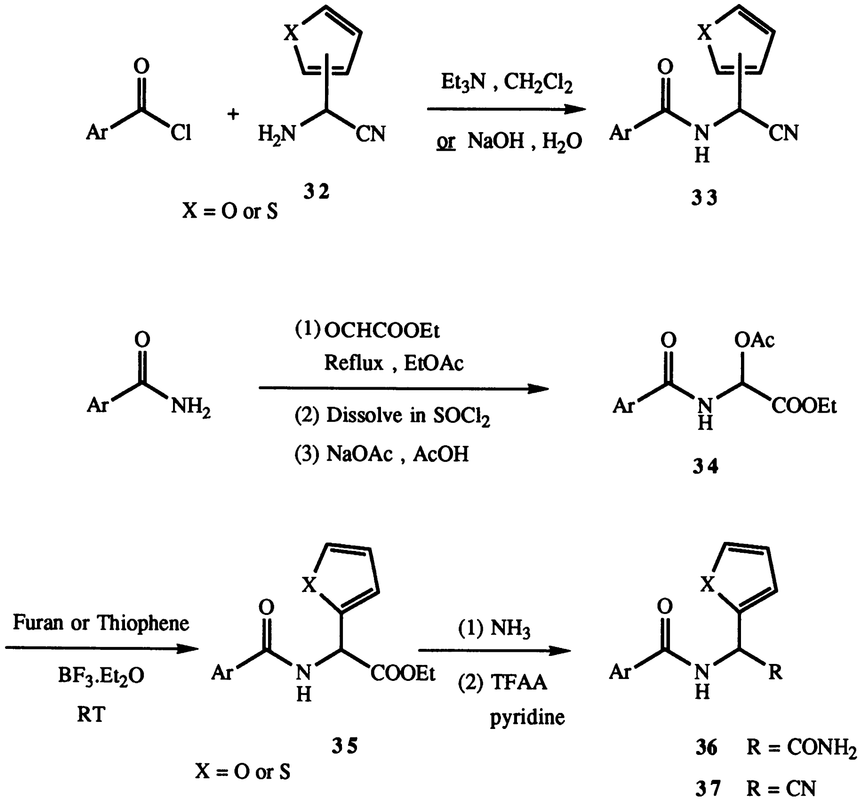

O
Ar
Cl
+
X
H2N
CN
32
X = O or S
Et3N , CH2Cl2
or NaOH , H2O
O
Ar
N
H
X
CN
33
O
Ar
NH2
(1) OCHCOOEt
Reflux , EtOAc
(2) Dissolve in SOCl2
(3) NaOAc , AcOH
O
OAc
Ar
N
H
COOEt
34
Furan or Thiophene
BF3.Et2O
RT
O
X
Ar
N
H
COOEt
35
X = O or S
(1) NH3
(2) TFAA
pyridine
O
X
Ar
N
H
R
36 R = CONH2
37 R = CN

Figure 10

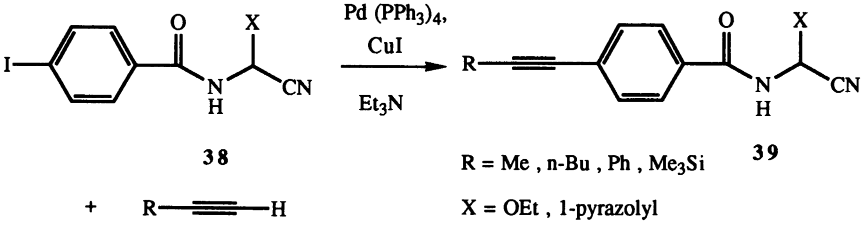

I
O
X
N
H
CN
38
+ R—≡—H
Pd (PPh3)4,
CuI
Et3N
R
O
X
N
H
CN
39
R = Me , n-Bu , Ph , Me3Si
X = OEt , 1-pyrazolyl

Figure 11

In Synthesis and Chemistry of Agrochemicals III; Baker, D., et al.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1992.

that there was no cross resistance to the phenyl amides. Attempts to generate resistant mutants by either adaptation or mutagenesis failed. Consequently it was believed that the likelihood of resistance developing was relatively small.

Conclusion

Speculative chemistry around a novel heterocyclic intermediate led to the discovery of a new class of fungicidal structure with high activity on Oomycete pathogens. From this work ICIA0001 was chosen for commercial develoment, due to its excellent control of *Plasmopara viticola* and other Oomycetes in the field, and its very safe environmental profile.

Unfortunately, the commercialisation of ICIA0001 was halted when unexpected toxicity occurred very late in two year feeding trials. No effects had been seen in any of the early *in vitro* and *in vivo* tests.

Notwithstanding this result, the discovery of this new type of benzamide fungicide provides an interesting example of the successful application of a speculative chemical approach to the invention of agrochemicals.

Acknowledgments

The authors are indebted to the following colleagues for their work on this project: Dr. S. P. Heaney and Dr. M. C. Shepherd for biological screening; Dr. B. C. Baldwin for biochemical studies; T. E. M. Fraser for physical chemistry studies; R. Cheetham, S. E. Evans, S. E. Glue, L. G. Reynolds, I. T. Streeting, E. G. Williams and J. Williams for experimental assistance; Dr. A. T. Costello and Dr. J. D. Jones for process chemistry; and P. K. Carpenter for chiral chromatography.

Literature Cited

1. Bartholomew, D.; Kay, I. T. *J. Chem. Research.* **1977**, 237.
2. Bartholomew, D.; Kay, I. T. *J. Chem. Research.* **1977**, 239.
3. McNulty, P. J.; Swithenbank, C.; Viste, K. L. *J. Agr. Food Chem.* **1971**, 417-421.
4. Crowley, P. J.; Heaney, S. P.; Shearing, S. J.; Shephard, M. C. *Proc. Br. Crop Prot. Conf. Pest Dis.* **1988**, 551-558.
5. Bartholomew, D.; Kay, I. K.; Noon, R. A.; Williams, E. G. European Patent 59536, **1982**.
6. Jones, J. D.; Schofield, D. European Patent 135304, **1984**.
7. Costello, A. T.; Jones, J. D. European Patent 260801, **1987**.
8. Crowley, P. J.; Heaney, S. P.; Reynolds, L. G.; British Patent 2183639, **1987**.
9. Young, D.H. *Pestic. Biochem. and Physiol.* **1991**, 149-161.
10. Droughot, V.; Gredt, M.; Leroux, P. *Pestic. Sci.* **1990**, 348.
11. Eacott, C.J.P. *PhD. Thesis, University of London* **1986**.
12. Hanaue, M.; Mita, T.; Nishikubo, M.; Ochciai, Y.; Suzuki, H.; Takeyama, T.; Yamagishi, K. European Patent 268892, **1988**.

RECEIVED June 1, 1992

Downloaded by PENNSYLVANIA STATE UNIV on June 20, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ch040

Author Index

Ackermann, P., 395
Ackmann, Stephen A., 200
Addor, Roger W., 283,306
Ahmed, Z. H., 226
Akagi, T., 43
Ali, Syed F., 313
Allgood, Sarah G., 147
Alvarado, S. I., 75
Andrea, Tariq A., 91
Arnason, John, 349
Asato, G., 226
Atkinson, Jeffrey, 349
Babcock, T. J., 283,298
Babczinski, Peter, 103
Baker, Don R., 1
Barden, T. C., 226
Bartholomew, David, 443
Basarab, Gregory S., 414
Baum, Jonathan S., 134
Beck, James R., 200
Berard, D. F., 336
Black, B. C., 283
Boeck, LaVerne D., 214
Brady, T. E., 75
Bravo, Héctor R., 349
Brown, D. G., 283
Buckwalter, B. L., 226
Burkart, Susan E., 258,271
Campos, Francisca, 349
Carson, C. M., 17
Charumilind, Pana, 147
Chio, Eddie H., 214
Chupp, John P., 161
Clark, Robert D., 147
Clough, John M., 372
Costales, Mark J., 10,17,26
Crews, A. D., 75
Crowley, Patrick J., 443
Cullen, Thomas G., 258,271,313,361
Davis, George E., 200
de Fraine, Paul J., 372
Deeter, Jack B., 214
Dell, Ian, 384
Denes, L. Radu, 91
DiSanzo, Carmen P., 361
Diehl, R. E., 283,298
Doehner, R. F., 75
Doney, J. J., 17
Dreikorn, B. A., 336,342
Engel, John F., 258,271
Fenyes, Joseph G., 1
Finkelstein, Bruce L., 91
France, D. J., 226
Fraser, Torquil E. M., 372
Frei, Bruno, 239
Fuesler, Thomas P., 91
Furch, J. A., 283,298
Gaede, Bruce J., 147
Gange, D. M., 75
Gerwick, B. Clifford, 10,17,26
Godfrey, Christopher R. A., 372,384
Goure, William F., 161
Greenplate, John, 327
Guaciaro, M. A., 56
Hackler, R. E., 109
Haga, T., 43
Hamada, Tatsuhiro, 103
Harper, R. W., 336
Heim, Dale R., 200
Holtwick, J. B., 10,17
Hotzman, Frederick W., 122,134
Huber, Marie-Luise, 186
Humphreys, W. H., 342
Huppatz, John L., 186
Johnson, Curt B., 414
Kameswaran, V., 226,283,306
Kamhi, V. M., 283,298
Kaster, S. V., 109
Kawamura, Shinichi, 103
Kay, I. Trevor, 443
Kirst, Herbert A., 214
Kleschick, William A., 10,17,26
Knüppel, P. C., 405
Kramer, K. E., 336,342
Kranis, Kevin T., 414
Kremer, K. A., 283
Kuhn, D. G., 283,298
Kurtzweil, Mitchell L., 147
Langevine, Charles M., 258
Lantzsch, R., 405
Lavrik, Paul B., 327
Leschinsky, Kindrick L., 161

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix001

Lew, Albert C., 271
Little, D. L., 56,75
Little, J. C., 17
Livingston, Robert S., 414
Los, M., 56
Lovell, J. B., 283
Lowen, G. T., 283,298
Lyga, John W., 134
Lynch, Michael P., 200
Manfredi, Mark C., 134
Maravetz, Lester L., 134
Marc, P. A., 56
Marek, Francis L., 271,313
Martinez, Anthony J., 361
McCaffery, Leslie F., 186
McFadden, Helen G., 186
Meier, Gary A., 258,271,313
Meikle, R. W., 10,17
Michel, Karl H., 214
Miller, T. P., 283
Mischke, Deborah A., 147
Moedritzer, Kurt, 147
Mollet, J. A., 336,342
Monte, W. T., 10,17
Morimoto, K., 34
Murai, S., 43
Mynderase, Jon S., 214
Nakamura, Y., 43
Nakasukasa, Walter M., 214
Nawamaki, T., 34
Niemeyer, Hermann M., 349
Nyfeler, R., 395
O'Sullivan, Anthony C., 239
Occlowitz, John L., 214
Parker-Jackson, E., 226
Parlow, John J., 147
Paschal, Jonathon W., 214
Pearson, N. R., 10,17
Peevey, R. M., 283
Poss, Kathleen M., 134
Prisbylla, Michael P., 177
Quakenbush, L., 56
Ray, Partha S., 313
Rogers, Michael D., 147
Sakashita, N., 43
Sandmann, Gerhard, 103
Sanemitsu, Yuzuru, 103
Sato, Ryo, 103
Sato, T., 34
Scherer, Lynn W., 122
Sehgel, Saroj, 258
Selby, Thomas P., 91
Siddens, J. K., 283
Sieburth, Scott M., 258,271
Silverman, I. Robert, 313
Singh, Rajendra K., 147
Smith, Ben K., 91
Smith, Bruce A., 122
Snider, S. W., 10,17
Staszak, Michael A., 200
Steffens, James J., 1
Stikes, Gina L., 147
Strickland, James H., 271
Subramanian, M. V., 10,17
Tamura, S. Y., 226
Tao, E., 336
Theodoridis, George, 122,134
Thompson, Gary D., 214
Thompson, L. G., 336
Treacy, M. F., 283
Trotto, S. H., 283,298
Tschabold, Edward E., 200
Tseng, S-S., 226
Tymonko, John M., 122,134
VanHeertum, J. C., 10,17
Vinogradoff, A. P., 10,17
Vollmer, Steven J., 414
Wadsworth, David J., 384
Waldrep, T. W., 109
Ward, R. K., 306
Webber, R. Keith, 147
Webster, Charles A., 313
Wee, Siok-Hui, 177
Wepplo, P. J., 75
Wilkes, Marty C., 327
Willut, James M., 361
Wilson, Kenneth R., 134
Wollweber, D., 405
Woolard, Frank X., 81
Wratten, Stephen J., 161
Wright, D. P., Jr., 283
Wright, Fred L., 200
Wyle, Michael J., 122,134
Yamaguchi, H., 428
Yamaguchi, M., 428
Yamaki, H., 428
Yamamoto, S., 34
Yao, Raymond C., 214

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix001

Affiliation Index

American Cyanamid Company, 56,75,226,283,298,306
Bayer AG, 103,405
Buckman Laboratories International, Inc., 1
Ciba-Geigy Ltd., 239,395
Commonwealth Scientific and Industrial Research Organisation, 186
DowElanco, 10,17,26,109,200,214,336,342
E. I. du Pont de Nemours and Company, 1,91,414
Eli Lilly and Company, 200,214,336
FMC Corporation, 122,134,258,271,313,361
ICI Agrochemicals, 372,384,443
ICI Americas Inc., 1,81,177
Ishihara Sangyo Kaisha, Ltd., 43
Monsanto Agricultural Company, 147,161,327
Nissan Chemical Industries, Ltd., 34
Sumitomo Chemical Company Ltd., 103
Universität Konstanz, 103
University of Ottawa, 349
University of Tokyo, 428

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix001

Subject Index

A

A83543, characterization, culture broths, and factors, 215–223
A83543A, characterization and biosynthesis, 217–220,222–223
AC 303,630, insecticidal activity, 295–296
2-Acylaminothiazolidines, structure–bleaching activity relationship, 87–88
Agrochemical(s)
  discovery approaches, 443
  discovery designs, 5
  environment for new chemicals, 2
  resistance, 4–5
  risk vs. benefit, 2–4
Agrochemical safety, costs of regulation, 4
Algicidal activity, isothiazoleureas, 118,119–120*t*
Alkoxy heterocyclic substitution, effect on biological activity and soil decomposition of 1,2,4-triazolo[1,5-*a*]-pyrimidine-2-sulfonanilides, 17–25
Alkoxy-substituted 1,2,4-triazolo[1,5-*a*]-pyrimidine-2-sulfonanilides
  biological activity tests, 21,23–25*t*
  synthesis, 17–22
2-Alkoxytriazolo[1,5-*a*]pyrimidines, synthesis, 92,95*f*
Alkyl substitution, effect on biological activity of 1,2,4-triazola[1,5-*a*]-pyrimidine-2-sulfonanilide, 10–16
Alkyldinitrodiphenylamines
  miticidal activity, 344,345–347*t*
  structure–activity relationships, 343–344
13β-Alkylmilbemycins
  biological activity, 255
  regioselectivity of alkylation, 248–251*t*
  synthesis, 247,248*f*
N-Alkyl-substituted thiazoles, synthesis, 328,330,331*f*
Amines with aliphatic side chains
  fungicidal activity, 423,424*t*
  reductase inhibition, 423,424*t*
Amino acids, inhibition of biosynthesis by RI–331, 432*t*,434
2-Amino-4-oxo-5-hydroxypentanoic acid, *See* RI–331
α-Aminosulfonylcarboxamides, synthesis of sulfonylcarboxamides, 77
3-Amino-1,2,4-triazoles, reaction with phenyl-1,3-diketones, 92,93*f*
1-Aryl-5-(aminocarbonyl)-1*H*-pyrazole-4-carboxylic acids
  gametocidal activity, 208,209*t*,210*f*
  synthesis, 202–209
2-Aryl-4-bromo-5-(trifluoromethyl)pyrrole-2-carbonitriles, insecticidal activity, 302,303*t*
3-Aryl-4-bromo-5-(trifluoromethyl)pyrrole-3-carbonitriles, insecticidal activity, 303,304*t*
1-Aryl-5-chloro-1*H*-pyrazole-4-carbonitriles, synthesis, 202*f*

Affiliation Index

American Cyanamid Company, 56,75,226,283,298,306
Bayer AG, 103,405
Buckman Laboratories International, Inc., 1
Ciba-Geigy Ltd., 239,395
Commonwealth Scientific and Industrial Research Organisation, 186
DowElanco, 10,17,26,109,200,214,336,342
E. I. du Pont de Nemours and Company, 1,91,414
Eli Lilly and Company, 200,214,336
FMC Corporation, 122,134,258,271,313,361
ICI Agrochemicals, 372,384,443
ICI Americas Inc., 1,81,177
Ishihara Sangyo Kaisha, Ltd., 43
Monsanto Agricultural Company, 147,161,327
Nissan Chemical Industries, Ltd., 34
Sumitomo Chemical Company Ltd., 103
Universität Konstanz, 103
University of Ottawa, 349
University of Tokyo, 428

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

Subject Index

A

A83543, characterization, culture broths, and factors, 215–223
A83543A, characterization and biosynthesis, 217–220,222–223
AC 303,630, insecticidal activity, 295–296
2-Acylaminothiazolidines, structure–bleaching activity relationship, 87–88
Agrochemical(s)
  discovery approaches, 443
  discovery designs, 5
  environment for new chemicals, 2
  resistance, 4–5
  risk vs. benefit, 2–4
Agrochemical safety, costs of regulation, 4
Algicidal activity, isothiazoleureas, 118,119–120*t*
Alkoxy heterocyclic substitution, effect on biological activity and soil decomposition of 1,2,4-triazolo[1,5-*a*]-pyrimidine-2-sulfonanilides, 17–25
Alkoxy-substituted 1,2,4-triazolo[1,5-*a*]-pyrimidine-2-sulfonanilides
  biological activity tests, 21,23–25*t*
  synthesis, 17–22
2-Alkoxytriazolo[1,5-*a*]pyrimidines, synthesis, 92,95*f*
Alkyl substitution, effect on biological activity of 1,2,4-triazola[1,5-*a*]-pyrimidine-2-sulfonanilide, 10–16
Alkyldinitrodiphenylamines
  miticidal activity, 344,345–347*t*
  structure–activity relationships, 343–344
13β-Alkylmilbemycins
  biological activity, 255
  regioselectivity of alkylation, 248–251*t*
  synthesis, 247,248*f*
N-Alkyl-substituted thiazoles, synthesis, 328,330,331*f*
Amines with aliphatic side chains
  fungicidal activity, 423,424*t*
  reductase inhibition, 423,424*t*
Amino acids, inhibition of biosynthesis by RI–331, 432*t*,434
2-Amino-4-oxo-5-hydroxypentanoic acid, *See* RI–331
α-Aminosulfonylcarboxamides, synthesis of sulfonylcarboxamides, 77
3-Amino-1,2,4-triazoles, reaction with phenyl-1,3-diketones, 92,93*f*
1-Aryl-5-(aminocarbonyl)-1*H*-pyrazole-4-carboxylic acids
  gametocidal activity, 208,209*t*,210*f*
  synthesis, 202–209
2-Aryl-4-bromo-5-(trifluoromethyl)pyrrole-2-carbonitriles, insecticidal activity, 302,303*t*
3-Aryl-4-bromo-5-(trifluoromethyl)pyrrole-3-carbonitriles, insecticidal activity, 303,304*t*
1-Aryl-5-chloro-1*H*-pyrazole-4-carbonitriles, synthesis, 202*f*

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

2-Aryl-3-cyano(nitro)pyrroles, 286–288
2-Aryl-3-cyanopyrroles, 290–291
2-Aryl-3-cyano-5-(trifluoromethyl)pyrroles, pesticidal evaluation, 293,294*t*,295
2-Aryl-4,5-dihalopyrrole-3-carbonitriles, structure, 298
3-Aryl-4-[(dimethylamino)methyl]dihydropyrazoles, synthesis, 318–319
2-Aryl-4-halo-5-(trifluoromethyl)pyrrole-3-carbonitriles, insecticidal activity, 302,303–304*t*
3-Aryl-4-[(methylsulfonyl)methyl]dihydropyrazoles, synthesis, 318–320
1-Aryl-1*H*-pyrazole-4,5-dicarbonitriles, synthesis, 202*f*
1-Aryl-4-substituted-1,4-dihydro-5*H*-tetrazol-5-ones
  general structure, 122,123*f*
  microbial transformations, 132*f*
  structure–activity relationships, 123–124,126,128–131*f*
  syntheses, 124,125–128*f*
N-Arylsulfonylhydantoins, synthesis of sulfonylcarboxamides, 78
N-Arylsulfonylimidazolinones, synthesis of sulfonylcarboxamides, 76–77
1-Aryl-1,2,4-triazolin-5-ones
  structure–herbicidal activity relationships, 138–145
  syntheses, 135–137*f*,139–141,143–144
2-Aryl-5-(trifluoromethyl)pyrrole-3-carbonitriles, synthesis, 299–301
3-Aryl-5-(trifluoromethyl)pyrrole-3-carbonitriles, synthesis, 302*f*
Aspartates, inhibition of biosynthesis by RI–331, 431–434
Auxin-transport inhibitors, structures, 177,178*f*
Avermectin B_{1a}, structure, 226–227,228*f*
Avermectins, 239–241
Azlactones, synthesis of sulfonylcarboxamides, 77–78

B

Benzamide fungicides, structure–activity relationships, 444–455
N-Benzoyl-*N*-alkyl-2-aminothiazoles
  cytochrome P-450 *N*-methyl oxidations, 330,333*f*,334
  synthesis, 327–331*f*
  toxicity, 330,332–334
Benzoylpyrroles, 286–288
Biological activity
  alkoxy heterocyclic substitution effect for 1-aryl-4-substituted-1,4-dihydro-5*H*-tetrazol-5-ones, 131*t*
  F28249 macrolides, 231,234,235–237
  LL-F28249, 231,234–237
  13β-substituted-milbemycins, 255
  1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonanilides, 17–25
Biosynthesis, A83543 factors, 220,222*f*,223
2,6-Bis(polyfluoromethyl)pyridine-3,5-dicarboxylates, 161–164
Bis(trifluoromethyl)pyrroles, 307–311
Bleaching herbicides
  phenyl-substituted five-membered-ring heterocycles, 81–90
  7-phenyl-1,2,4-triazolo[1,5-*a*]-pyrimidines, 91–101
Blue-sky research, use for discovery of agrochemicals, 443

C

Capsimycin, structure, 218,219*f*
1-Carbamoyl-3-aryl-4-(carboxymethyl)-4,5-dihydropyrazoles
  foliar activity, 321*t*,322
  syntheses, 315–316
1-Carbamoyl-3-aryl-4-cyanodihydropyrazoles, synthesis, 317–318
1-Carbamoyl-3-aryl-4,5-dihydropyrazoles, foliar activity, 324,325*t*
  syntheses, 317–320
1-Carbamoyl-3,4-diaryl-4,5-dihydropyrazoles, syntheses, 317
N-Carbamoyldihydropyridine-3,5-dicarboxylates, synthesis, 166*f*
Carotenoid biosynthesis, inhibition by phenyltriazolo[1,5-*a*]pyrimidines, 101*f*
CGA 142705, 401–403
Chemical hybridizing agents, discovery, 200
Chlorination, synthesis of pyrazole-5-sulfonamides, 39*f*
5-Chloro-1-aryl-*N*-methyl-1*H*-pyrazole-4-carboxamides, synthesis, 201*f*
4-Chloro-*N*-[cyano(ethoxy)methyl]benzamide, *See* ICIA0001

1-(4-Chloro-2-fluoro-5-ethylsulfonylamino-phenyl)-1,4-dihydro-4-(3-fluoropropyl)-5*H*-tetrazol-5-ones
  activity, 122–124,131–132
  synthesis, 124,125–128*f*
N-Chloroimidazolinones, 62,63*t*
N-(Chloromethyl)thiazoles, synthesis, 328,331*f*
3-(Chlorophenyl)-4-carboxy-1*H*-pyrazole-5-carboxamides, structures, 204,206*f*
1-(4-Chlorophenyl)-1-cyclopropyl-4-(3-phenoxyphenyl)butane
  biological testing procedure, 275,278
  structure, 272*f*
  synthesis, 273,274*f*,275,276–277*f*
  toxicity, 279,281–282
2-(4-Chlorophenyl)-4-halo-5-(trifluoromethyl)-pyrrole-3-carbonitriles, insecticidal activity, 303,304*t*
Chloropyrrole, light stability, 401*f*
Cyanoacrylate inhibitors of photosynthetic electron transport, structure–activity relationships, 188–196
2-Cyanoacrylic acid esters, 187
5-Cyano-1-aryl-*N*-methyl-1*H*-pyrazole-4-carboxamides, synthesis, 202,203*f*
3-Cyano-4-arylpyrroles, substituent vs. fungicidal activity, 397–398*t*
N-Cyanoimidazolinones
  biological activity of acid salts, 69,71–73
  degradation pathways, 64,65*f*
  herbicidal activity of esters, 64,66–70
3-Cyano-4-phenylpyrroles
  activity, 397–400,402–403
  toxicological properties, 401*t*
Cyclic hydroxamic acids, synthesis and properties, 350–359
Cyclization, synthesis of pyrazole-5-sulfonamides, 37,38*f*
Cyclopentylamine diastereomers, 421,423–425
1-Cyclopropyl-1-(4-*X*-phenyl-4-(4-*Y*-3-phenoxyphenyl)butanes, foliar activity, 278*t*,279
1-Cyclopropyl-1-(4-substituted-phenyl)-4-(4-fluoro-3-phenoxyphenyl)butane, structure, 271,272*f*
Cytochrome P-450 *N*-methyl oxidations, 330,333*f*,334

D

DE-498
  biological activity, 14,15*t*
  crop selectivity, 30–31,32*f*
  crop tolerance, 14–16
  function, 17,26
  structure, 26*f*
1,5-Diaryl-3-carbamoyl-4,5-dihydropyrazoles
  foliar activity, 322*t*
  syntheses, 315–317
1,4-Diaryl-1-cyclopropylbutanes
  activity and toxicity, 278–282
  biological testing procedure, 275,278
  structures, 272–273
  synthesis, 273–277*f*
Diazotization, synthesis of pyrazole-5-sulfonamides, 35,36–37*f*
1-[2,4-Dichloro-5-[*N*-(methylsulfonyl)amino]-phenyl-1,4-dihydro-3-methyl-4-(difluoromethyl)-5*H*-triazol-5-one, *See* F6285
Dihalopyrroles, structure, 298
Dihydropyrazoles, activity and structures, 313–315
Dihydropyrazoles with reduced lipophilicity
  biological testing procedure, 320–321
  development procedure, 314
  insecticidal activity, 321–325*t*
  structure–activity analyses, 322–324
  syntheses, 315–320
1,2-Dihydropyridine-3,5-dicarboxylates, structure–herbicidal activity relationships, 161–164
2,4-Dihydroxy-7-methoxy-1,4-benzoxazin-3-one
  acid–base properties, 353–354
  mode of action in European corn borer, 356–358
  protease inhibition, 358
  reactions, 355–356
  role in crop protection, 358–359
  synthesis via reductive cyclizations, 350,352*f*
Dimethyl 2-(difluoromethyl)-4-isopropyl-6-(trifluoromethyl)pyridine-3,5-dicarboxylates, herbicidal activity, 166–168*t*
Dinocap, uncoupling of oxidative phosphorylation, 285*f*

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

- Dioxapyrrolomycin
  - insecticidal and miticidal activity, 284*f*
  - isolation, 284,306
  - structure, 284*f*,298,306*f*
- Diphenylamines
  - structure–miticidal activity relationships, 338,340*t*,344–347*t*
  - synthesis, 337–338,343
- Diphenylpyridines
  - biology test method, 104,106
  - bleaching herbicidal activity, 103
  - general structure, 103–104
  - structure–activity relationships, 106–108
  - syntheses, 104–105
- Discovery designs, approaches, 5
- 1,2-Dithiolo[4,3-*b*]pyrrolones, naturally occurring, *See* Naturally occurring 1,2-dithiolo[4,3-*b*]pyrrolones

E

- EL–462
  - comparative phytotoxicity of *N*-H vs. *N*-alkyl compounds, 338,340*t*
  - miticidal activity, 336,338–339,341
  - structure–activity relationships, 336–338
  - synthesis of analogs, 337–338
- Epoxycyclopentylamines
  - fungicidal activity, 423,424*t*
  - optimized structures, 423,426*f*
  - reductase inhibition, 423,424*t*
  - syntheses, 418–420*f*
- Ethofenprox, structure, 271,272*f*
- 13β-Ethylmilbemycin A_4, synthesis, 248*f*

F

- F6285
  - herbicidal activity, 134,135,143
  - structure and synthesis, 134–137*f*
- F28249, structure, 227,228*f*
- F28249 macrolides
  - biological activity, 231,234–237
  - epoxide derivative biological activity testing, 234,235*t*
  - LL-F28249 biological activity, 234,237
  - mite control on cotton, 234,236*t*
  - protection strategies, 227–230*f*
  - silylation regioselectivity, 227–229
  - substitutions, 229–236
- F28249α, isolation, 227
- Fenazaflor, uncoupling of oxidative phosphorylation, 285*f*
- Fenpiclonil, properties, 401–403
- Fentrifanil, uncoupling of oxidative phosphorylation, 285*f*
- Fenvalerate, structure–activity relationships, 271–273
- Fermentation broths, screening as method of discovery of compounds with biological activity, 214
- Fermentation products, importance of screen development for discovery, 215
- Fish toxicity, 1,4-diaryl-1-cyclopropylbutanes, 281*t*
- Flumetsulam, *See* DE–498
- Fluorochloridone, structure, 81,82*f*
- 13-Fluoromilbemycins
  - mechanism of formation, 243,244–245*f*
  - synthesis, 241,242*f*
- 13β-Fluoromilbemycins, biological activity, 255
- Foliar activity, 1,4-diaryl-1-cyclopropylbutanes, 278*t*,279
- Fumigants, use for chemical control of nematodes, 361
- Fungicidal activity
  - amines with aliphatic side chains, 423,424*t*
  - cyclopentylamine diastereomers, 424,425*t*
  - epoxycyclopentylamines, 424
  - β-methoxyacrylates, 372–383
  - phenylpyrroles, 411,412*t*
  - pyrrolnitrin, 396
  - pyrrolnitrin analogs, 411,412*t*
- Fungicides, discovery methods and reasons for development, 372

G

- Gametocidal activity, 1-aryl-5-(aminocarbonyl)-1*H*-pyrazole-4-carboxylic acids, 208–210*f*

H

- Halo substitution, effect on biological activity of 1,2,4-triazola[1,5-*a*]pyrimidine-2-sulfonanilide, 10–16
- Haloalkoxytriazolo[1,5-*a*]pyrimidines, 92,95*f*

Haloalkyl substitution, effect on biological activity of 1,2,4-triazola[1,5-*a*]pyrimidine-2-sulfonanilide, 10–16
13β-Halomilbemycins, synthesis, 245,246*f,t*
Herbicidal activity
  1-aryl-4-substituted-1,4-dihydro-5*H*-tetrazol-5-ones, 126,128–130*f*
  1-aryl-1,2,4-triazolin-5-ones, 143,145*t*
  2-cyanoacrylates, 195,196*t*
  isomeric 1-phenyl-2,4-imidazolidinediones, 184*t*
  isothiazoleureas, 112–118
  phenoxypyrazoles, 159
  pyrazole phenyl ethers, 159
  pyrazole-5-sulfonylureas, 40–41*t*
  5-substituted-2,4-imidazolidine-diones, 180
  N-substituted-imidazolinones, 56–73
  N-substituted-2,6-(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates, 166–175
  sulfonylcarboxamides, 78–79
Hill reaction activity, 2-cyanoacrylates, 189–195
Holomycin analogs, synthesis, 389,391–392
Homoserine dehydrogenase, inhibition by RI-331, 434–439
Hybridization of plants, 200
Hydroxamic acids
  correlation of levels with insect resistance, 349
  cyclic, 350–359
N-Hydroxyimidazolinones, biological activity and synthesis, 57–61

I

ICIA0001
  biological activity, 449
  mode of action, 453
  resistance properties, 453,456
  structure, 449,450*f*
Ikarugamycin, structure, 218,219*f*
Imidazolidones
  structure–bleaching activity relationship and synthesis, 85–87
  substitution vs. herbicidal activity, 56
Imidazolinone herbicides, importance, 10
Industrial pesticide research progress, market forces, 327
Insect control, specificity requirement, 283
Insecticidal activity
  N-benzoyl-*N*-alkyl-2-aminothiazoles, 330,332*t*
  dihydropyrazoles with reduced lipophilicity, 321–325*t*
  trifluoromethyl-substituted arylpyrrolecarbonitriles, 302,303–304*t*
Insecticidal pyrroles
  bis(trifluoromethyl)pyrroles, 306–311
  dihydropyrazoles with reduced lipophilicity, 313–325
  discovery, 283,284–285*f*
  pesticidal evaluation, 285–296
  synthesis, 286,287*f*,290*f*,292*f*
  trifluoromethyl-substituted arylpyrrolecarbonitriles, 298–304
  uncoupling of oxidative phosphorylation, 284–286
Insecticides
  importance of discovery, 215
  selectivity improvements, 327
Interceptor, development and structure, 239–240
Isomeric aryl(cyano)pyrroles
  pesticidal evaluation, 292–294*t*
  synthesis, 292*f*
Isomeric 1-phenyl-2,4-imidazolidinediones, herbicidal activity, 184*t*
Isothiazoleureas
  classification, 109–110
  crop selectivity, 112,117*t*,118
  modes of action, 111–112
  structure–activity relationships, 109–120
  synthesis, 110
Ivermectin
  biological activity, 255
  structure, 239,240*t*

L

Lithiation, synthesis of pyrazole-5-sulfonamides, 36,37*f*
LL-F28249
  biological activity, 231,234–237
  protection strategies, 227–230*f*
  synthetic modification, 229–233
LL-F42248α, isolation and structure, 306

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

M

Macrolides, structural and biological diversity, 214
Maize, insect resistance, 349
Male sterility in crops, chemical and mechanical methods, 200
Mammalian toxicity
  N-benzoyl-*N*-alkyl-2-aminothiazoles, 330,333*f*
  1,4-diaryl-1-cyclopropylbutanes, 282*t*
  dihydropyrazoles, 314,315*t*
β-Methoxyacrylates, natural, *See* Natural β-methoxyacrylates
6-Methoxy-1,3-benzoxazin-2-one, structure, 349,350*f*
Methylcyclopentylamine diastereomers, synthesis, 417*f*
N-Methyl-2,4-difluoro-2′,4′-dinitro-6′-(trifluoromethyl)diphenylamine, *See* EL–462
4-(Methylsulfonyl)dihydropyrazoles, synthesis, 320
1-Methyl-3-(trifluoromethyl)-5-hydroxypyrazole, synthesis, 147,148*f*
Microbial transformations, 1-(4-chloro-2-fluoro-5-ethylsulfonylaminophenyl)-1,4-dihydro-4-(3-fluoropropyl)-5*H*-tetrazol-5-ones, 132*f*
Milbemycin(s)
  activity and discovery, 226–227
  isolation, 239
  structures, 226,239–241
  13β-substituted, *See* 13β-Substituted-milbemycins
Milbemycin D, structure, 226,228*f*
Miticidal activity
  alkyldinitrodiphenylamines, 344,345–347*t*
  EL–462 analogs, 338,339*t*
Mixed anhydrides, synthesis of sulfonylcarboxamides, 78
Mode of action of hydroxamic acids in European corn borer, 356–358
Mosquito larvicidal activity
  A83543 factors, 220
  indicator assay for other insecticidal activities, 215
MTI–800, structure, 271,272*f*
Myxothiazol, fungicidal activity and structure, 373,375*f*

N

Natural β-methoxyacrylates
  fungicidal activity, 373
  production of synthetic fungicides, 373–383
  structures, 373,375*f*
Natural products, role in development of pharmaceutical products and agrochemicals, 384
Naturally occurring 1,2-dithiolo[4,3-*b*]-pyrrolones
  structures, 385,387*f*
  syntheses, 386–392
NC–319
  herbicidal activity, 40,41*t*
  synthesis, 36–37,39
Nematicidal activity, 5-substituted-2-*S*-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles, 361–369
Nematicides, 361–362
Nematodes, chemical control agents, 361
Niclosamide, uncoupling of oxidative phosphorylation, 285*f*
Nicosulfuron, *See* SL–950 and analogs
Non-ester pyrethroid insecticides
  aquatic safety, 266,269*t*
  biological testing procedure, 261–263
  mammalian toxicity, 266,268*t*
  structure–activity relationships, 263–268
  synthesis, 259–262
Nonvolatile contact materials, use for chemical control of nematodes, 361

O

Oudemansin A
  diphenyl ether analog vs. fungicidal activity, 380–382
  fungicidal activity, 373
  phenoxy substituent vs. fungicidal activity, 376,380*t*,381
  ring nitrogen substitution vs. fungicidal activity, 381–383
  structure, 373,375*f*
Oudemansin A analogs
  photochemical degradation, 376,377*f*
  styryl group replacement with phenoxy group, 376,378–379*f*
  synthesis, 374,375*f*

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

Oxabicyclo[3.1.0]hexanamines, syntheses, 418–420*f*
N-Oxidation of lactams, synthesis of cyclic hydroxamic acids, 353,354*f*,*t*
Oxidative phosphorylation, uncouplers, 284,285*f*,286

P

Pest management, need for new plant protection chemicals, 395
Pest resistance, concern, 4–5
Phenoxypyrazoles
  germination assays, 150*t*,151
  mode of action, 151
  molecular modeling, 151,152*f*
  single-crystal X-ray structure determination, 151,153*f*
  structure–herbicidal activity relationships, 154,158–159
  syntheses, 149,150*f*,154–159
1-Phenyl-1,4-dihydro-5*H*-tetrazol-5-ones, structure, 122,123*f*
Phenyl-1,3-diketones, reaction with 3-amino-1,2,4-triazoles, 92,93*f*
2-Phenyliminopyrrolidines, structure–bleaching activity relationship, 87,88
2-Phenyliminothio(oxa)zolidines, structure–bleaching activity relationship, 85–87
Phenylpyrroles, fungicidal activity and syntheses, 408–412
4-Phenylpyrroles
  structure–fungicidal activity relationships, 396–399*f*
  synthesis using *p*-toluenesulfonyl methylcyanide, 396*f*
Phenyl-substituted five-membered-ring heterocycles, two-dimensional structure–activity space, 81–90*f*
Phenyltriazolo[1,5-*a*]pyrimidines, syntheses, 92,94*f*
7-Phenyl-1,2,4-triazolo[1,5-*a*]pyrimidines
  cereal field testing, 100
  chemistry, 92–98
  herbicidal activity, 98–101
Photosynthesis, target for herbicidal design, 186
Photosystem II inhibitors
  developments, 186–187
  examples, 196–197
Plant pathogenic fungi, growth inhibition by RI–331, 436,440*f*
Preemergence herbicidal activity, triazolopyrimidines, 98–99
Propyzamide, structure, 444,446*f*
Protection, role of hydroxamic acids, 358–359
Protein biosynthesis, preferential inhibition by RI–331, 429,431–439
Pyrazole amide acids
  activity, 202,204–206,208–210
  second-generation gametocides, 208,210*f*
  synthesis, 202–204,207–209
Pyrazole herbicides and gametocides, synthesis, 200,201*f*
Pyrazole phenyl ethers, *See* Phenoxypyrazoles
Pyrazole precursors, regioselective syntheses, 148*f*,149
Pyrazole *N*-substituted-carboxamide acids, synthesis, 204,205*f*
Pyrazole-5-sulfonylureas
  herbicidal activity, 40–41*t*
  synthesis, 34–39
Pyrazolo[1,5-*a*]pyrimidines, synthesis, 92,97*f*,98
Pyrethroid insecticides, non-ester, *See* Non-ester pyrethroid insecticides
Pyrethroids, advantages for use as insecticides, 258
Pyridine-3,5-dicarboxylates
  discovery and development, 161
  structure–herbicidal activity relationship, 162,163*f*
Pyridines, herbicidal activity, 103
Pyridylsulfonylurea herbicides
  quantitative structure–activity relationships, 49–53
  synthesis, 43–48
Pyrrolidines
  structure–bleaching activity relationship, 88
  synthesis, 88,89*f*
Pyrrolidones
  structure–bleaching activity relationships, 82–85*f*
  synthesis, 82
Pyrrolnitrin
  fungicidal activity, 396,406
  structure, 395,396*f*,405

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

Pyrrolnitrin—*Continued*
  synthesis using *p*-toluenesulfonyl methylisocyanide, 396*f*
Pyrrolnitrin analogs
  decomposition, 406–408
  fungicidal activity, 411,412*t*
  syntheses, 408–411
Pyrrolomycins
  pesticidal evaluation, 286–296
  synthesis, 286,287*f*,290*f*,292*f*
  uncoupling of oxidative phosphorylation, 284–286
Pyrrothines, biological activity, 385

Q

Quantitative structure–activity relationship model, nematicidal activity of 5-substituted-2-*S*-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiazoles, 362–368
Quantitative structure–activity relationships of SL–950 analogs
  interpretation of analyses, 54
  least-squares method, 49,52
  physical–chemical parameters, 49,50–53*t*

R

R–25788, formation of R–37878, 81
R–37878, synthesis, 81
Racemic ether synthesis, non-ester pyrethroid insecticides, 259–260
Reactivity, cyclic hydroxamic acids, 353,355–356
Reductase inhibition, 421,423–424
Reductive cyclizations, synthesis of cyclic hydroxamic acids, 350,352*f*
Regioselective syntheses, pyrazole precursors, 148*f*,149
Regulation of agrochemicals, costs, 4
Resistance, concern, 4–5
Resolved ether synthesis, non-ester pyrethroid insecticides, 261–262
RI–331
  fungicidal activity, 428–429
  growth inhibition of plant pathogenic fungi, 436,440*f*
RI–331—*Continued*
  inhibition of homoserine dehydrogenase, 434–439
  inhibition of radiolabeled precursor incorporation, 429*t*,431
  preferential inhibition of protein biosynthesis, 429,431–439
  structure, 428,430*f*
  therapeutic efficacy of oral treatment regimens, 428–429,430*f*
Risks, creation of new risks and problems, 2–3
Rye, insect resistance, 349

S

Safety, costs of regulation, 4
SL–950 and analogs
  coupling processes for synthesis, 48
  quantitative structure–activity relationships, 49–54
  structure, 43,44–45
  synthetic routes of precursors, 43,46–47
Soil decomposition, alkoxy heterocyclic substitution effect for 1,2,4-triazolo-[1,5-*a*]pyrimidine-2-sulfonanilides, 17–25
Speculative chemistry, use for discovery of agrochemicals, 443
Spiramycin, structure, 218,219*f*
Sterol biosynthesis, inhibition as disease control strategy, 414
Sterol dienes, microsomal reduction, 415,416*f*
Sterol reductase inhibitors, design, 414–426
Strobilurin A, activity and synthesis, 373–377
Strobilurin A analogs
  photochemical degradation, 376,377*f*
  structure–activity relationships, 376,380–383
  styryl group replacement with phenoxy group, 376,378–379*f*
  synthesis, 374,375*f*
Structure–activity relationships
  1-aryl-4-substituted-1,4-dihydro-5*H*-tetrazol-5-ones, 126,128–130*f*
  benzamide fungicides, 444,446*t*,447,448*f*,*t*
  sulfonylcarboxamides, 79
Structure–fungicidal activity relationships, 3-cyano-4-phenylpyrroles, 397–398*t*,399*f*

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

Structure–herbicidal activity relationships
  1-aryl-1,2,4-triazolin-5-ones, 138–143
  phenoxypyrazoles, 159
5-Substituted-2,4-imidazolidinediones
  connecting heteroatom vs. herbicidal activity, 181*t*
  herbicidal activity, 180
  initial synthetic route, 178*f*
  mode of action, 177
  structures, 177,178*f*
  substitutions, 181–183
  synthesis, 178–180*f*
2-Substituted-5-methyl-7-phenyltriazolo-[1,5-*a*]pyrimidines, preemergence herbicidal activity, 98*t*
2-Substituted-5-methyl-7-[(*m*-trifluoromethyl)phenyl]triazolo[1,5-*a*]pyrimidines, preemergence herbicidal activity, 98,99*t*
13β-Substituted-milbemycins
  13β-alkylmilbemycin synthesis, 247–251
  biological activity, 255
  synthesis, 241–254
  transition metal catalyzed synthesis, 251–254*f*,*t*
5-Substituted-2-*S*-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles
  biological testing procedure, 364–365
  correlation matrices, 362–363,365–368
  factor analysis, 362–366,368
  nematicidal activity, 369*t*
  physical–chemical data for translated set of analogs, 365,367*t*
  set selection, 362,363–364*t*
  structure–activity relationships, 365,366–368*t*
  target synthesis, 362,364
6-Substituted-triazolo[1,5-*a*]pyrimidines, synthesis, 92,94*f*
N-Substituted-dihydropyridine-3,5-dicarboxylates, synthesis, 164–166
N-Substituted-2-(fluorophenyl)-1,2,4-triazolo-[1,5-*a*]pyrimidine-2-sulfonanilides
  biological activity, 30,31*t*
  crop selectivity, 30–31,32*f*
  synthesis, 27–30*f*
N-Substituted-imidazolinones
  N-chloroimidazolinones, 62,63*t*
  N-cyanoimidazolinones, 62,64–73
  N-hydroxyimidazolinone synthesis, 57–61
  structures, 56
N-Substituted-2,6-(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates
  evidence of decomposition, 172–173*f*,174
  herbicidal activity, 166–175
  soil degradation products, 174,175*t*
  stability vs. pH, 174*t*
  substitution vs. activity, 166–172
  synthesis, 164,165–166*f*
N-Substituted-2-[(trifluoromethyl)phenyl]-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonanilides
  biological activity, 30,31*t*
  crop selectivity, 30–31,32*f*
  synthesis, 27–30*f*
Sulfonamides, synthetic routes, 43,46–48
Sulfonylcarboxamides
  discovery, 75–76
  herbicidal activity, 78–79
  synthesis, 76–78
Sulfonylurea herbicides
  importance, 10
  synthesis and herbicidal activity, 34–41
Synthesis
  alkyldinitrodiphenylamines, 343
  1-aryl-5-(aminocarbonyl)-1*H*-pyrazole-4-carboxylic acids, 202–209
  1-aryl-4-substituted-1,4-dihydro-5*H*-tetrazol-5-ones, 124,125–128*f*
  1-aryl-1,2,4-triazolin-5-ones, 135–137*f*
  benzamide fungicides, 444,445*f*
  N-benzoyl-*N*-alkyl-2-aminothiazoles, 328–331*f*
  bis(trifluoromethyl)pyrroles, 307–311
  N-carbamoyldihydropyridine-3,5-dicarboxylates, 166*f*
  1-(4-chlorophenyl)-1-cyclopropyl-4-(3-phenoxyphenyl)butane, 273–275,276–277*f*
  3-cyano-4-phenylpyrroles, 399,400*f*
  cyclic hydroxamic acids, 350–354
  cyclopentylamine diastereomers, 416,417*f*
  1,4-diaryl-1-cyclopropylbutanes, 273–275,276–277*f*
  dihydropyrazoles with reduced lipophilicity, 315–320
  EL-462 analogs, 337–338
  holomycin analogs, 389,391–392
  methylcyclopentylamine diastereomers, 417*f*

Downloaded by 89.163.35.42 on June 16, 2012 | http://pubs.acs.org
Publication Date: September 22, 1992 | doi: 10.1021/bk-1992-0504.ix002

- Synthesis—*Continued*
  - naturally occurring 1,2-dithiolo[4,3-*b*]-pyrrolones, 386–392
  - oxabicyclo[3.1.0]hexanamines, 418,420*f*
  - phenoxypyrazoles, 149,150*f*
  - phenylpyrroles, 408–411
  - pyrazole phenyl ethers, 149,150*f*
  - pyrazole-5-sulfonylureas, 35–39
  - pyridylsulfonylurea herbicides, 43–48
  - pyrrolnitrin analogs, 408–411
  - 5-substituted-2,4-imidazolidinediones, 178–180*f*
  - 13β-substituted-milbemycins, 241–254
  - *N*-substituted-dihydropyridine-3,5-dicarboxylates, 164–166
  - *N*-substituted-imidazolinones, 56–73
  - *N*-substituted-2,6-(polyfluoromethyl)-dihydropyridine-3,5-dicarboxylates, 164,165–166*f*
  - sulfonylcarboxamides, 76–78
  - thiolutin, 386,388–390
  - thiolutin analogs, 389–390
  - trifluoromethyl-substituted arylpyrrolecarbonitriles, 299–302*f*

T

- Tertiary amine fungicides
  - crystal structures, 421,422*f*
  - fungicidal activity, 424,425*t*
  - mode of fungicidal action, 414,415*f*
  - optimized structure, 425,426*f*
  - reductase inhibition, 421,423–424
  - relationship to sterol transition state, 415,416*f*
  - synthesis, 414,416–418
- Thioether synthesis, non-ester pyrethroid insecticides, 260–261
- Thiolutin
  - biological activity, 385
  - synthesis, 385–390
- Thiolutin analogs, synthesis, 389–390
- *p*-Toluenesulfonylmethylisocyanide, synthesis of pyrrolnitrin analogs, 396*f*
- Transition metal catalyzed synthesis, 13β-substituted-milbemycins, 251,253–254*f*,*t*
- Triazolo[1,5-*b*]pyridazines, synthesis, 92,96*f*
- Triazolo[1,5-*a*]pyridines, syntheses, 91–95,97*f*
- 1,2,4-Triazolo[1,5-*a*]pyrimidine-2-sulfonanilides
  - biological activity tests, 21,23–25*t*
  - biological testing, 14–16
  - in vivo and in vitro activity, 14–15,21,23*t*
  - soil half-lives vs. substitution, 21,23–25*t*
  - structures, 10,11*f*,17
  - synthesis, 10–22
- 2,4,6-Trichloro-2′-*tert*-butyl-4′,6′-dinitrodiphenylamine, miticidal activity, 342
- Trichloropyrroles, pesticidal evaluation and synthesis, 286
- 2-*S*-(3,4,4-Trifluoro-3-butenyl)-1,3,4-thiadiazoles, 5-substituted, *See* 5-Substituted-2-*S*-(3,4,4-trifluoro-3-butenyl)-1,3,4-thiadiazoles
- 2-(Trifluoromethyl)-7-phenyltriazolo[1,5-*a*]-pyrimidines, preemergence herbicidal activity, 98,99*t*
- Trifluoromethyl-substituted arylpyrrolecarbonitriles, insecticidal activity and synthesis, 299–304
- Trifluoromethyl-substituted pyrazoles, herbicidal activity, 147

V

- *O*-Vinyloximes, synthesis of bis(trifluoromethyl)pyrroles, 307

X

- Xenorhabdins, biological activity and structures, 385,387*f*

Production: Steven Powell
Indexing: Deborah H. Steiner
Acquisition: Cheryl Shanks and Anne Wilson
Cover design: Pat Cunningham

Printed and bound by Maple Press, York, PA